JUN 15 1923

VOLUME 25 NUMBER 6

AMERICAN JOURNAL

OF

DISEASES OF CHILDREN

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JUNE, 1923

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $4.00

Entered as Second-Class Matter, January 4, 1911, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

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American Journal of Diseases of Children

Vol. 25 JUNE, 1923 No. 6

THE IMPORTANCE OF COLOSTRUM TO THE NEW-BORN INFANT*

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The recent work of Smith and Little has definitely shown the importance of colostrum to the new-born calf. Not only is colostrum, according to Smith and his co-workers, the chief agent for transferring known antibodies to the new-born calf, but it seems to have also the important function of protecting the new-born animal of this species against a general invasion by organisms of the *B. coli* group which find their way into the intestinal tract during the first few days of life. These experiments which show so strikingly the value of colostrum to the new-born calf have again raised the question of the importance of colostrum to the human species.

SUMMARY OF RECENT WORK ON THE IMPORTANCE OF COLOSTRUM TO ANIMAL AND MAN

The concrete additions to our knowledge of the function of colostrum, made by Theobald Smith and his collaborators at the Rockefeller Animal Experiment Station, are as follows:

1. Little and Orcutt[1] have shown that calves born of cows which have become highly immune to *B. abortus* in the course of a natural infection with this organism have no agglutinins in their serums at birth. After the ingestion of colostrum, agglutinins appear in the serum of the calf and usually equal or even surpass the titer of the cow.

2. Howe[2] has shown that the blood of the new-born calf before the ingestion of colostrum is lacking both in pseudoglobulin and euglobulin. After the ingestion of colostrum, the globulin content rises rapidly as compared with that of the serum of calves that fail to receive colostrum.

3. Smith and Little[3] have shown that calves that fail to obtain colostrum succumb in from 75 to 80 per cent. of the cases to a generalized *B. coli* septicemia. In this experiment, the control colostrum-fed calves that were allowed to nurse for a very short time immediately after birth (fifteen minutes

* Received for publication, April 25, 1923.

* From the Department of Bacteriology and the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University.

1. Little, R. B., and Orcutt, M. L.: J. Exper. Med. **35**:161-171 (Feb.) 1922.
2. Howe, P. E.: J. Biol. Chem. **49**:115 (Nov.) 1921.
3. Smith, Theobald, and Little, R. B.: J. Exper. Med. **36**:181-198 (Aug.) 1922.

in one instance) survived; which indicates that a relatively small amount of colostrum is sufficient to prevent the invasion of *B. coli* in these animals.

4. In a subsequent paper, Smith and Little[4] have demonstrated that cow's serum may be substituted for colostrum.

In the various papers published by Theobald Smith and his co-workers, the conditions discovered by them in calves were not applied to the human species.

Interesting observations bearing on this subject have recently been published by Williams.[5] He finds that scours in the new-born calf is best avoided if the animal is allowed to nurse in the normal way. He assumes that this is due to antibodies present in the mammary secretion. (Williams does not differentiate between colostrum and milk.) This observer, however, maintains that the infection of the new-born calf which leads to fatal diarrhea takes place in utero instead of after birth, and the milk is of value largely because, in the course of the uterine infection, the mother has acquired a considerable increase of specific antibodies.

The work of Little and Orcutt, demonstrating the importance of colostrum in the transference of agglutinins to the new-born calves, was a corroboration of a similar series of experiments performed by Famulener[6] with goats in 1912. Famulener was the first investigator to emphasize the value of colostrum. His work differed from that of Little and Orcutt in that the goats used by him were artificially immunized with red blood cells during the course of pregnancy. He showed that the kids were born without hemolysins in their serum, and depended solely on the colostrum for transmission of these antibodies. In summing up his article, Famulener, from his work on goats, concluded that colostrum is equally important to the infant:

It follows from our observations that of all factors the colostrum plays the most important rôle in transmitting antibodies from the actively immunized mother to the young. Even under normal conditions, it is reasonable to suppose that protective substances are concentrated from the mother's body fluids and may be absorbed by the infant after the first feedings. Consequently, it seems of the highest importance that the newly born child should, during the first few days of life, receive the colostrum-milk unless contraindicated for some special reason.

Lewis and Wells,[7] in a recent article, have tried to determine the function of colostrum in the human species by a study of new-born infants.

They studied the globulin content of six different specimens of cord blood and found that, in contrast to the calf, the infant is born with a normal amount of pseudoglobulin, and is lacking only in euglobulin. They investigated the

4. Smith, Theobald, and Little, R. B.: J. Exper. Med. **36**:453-468 (Oct.) 1922.

5. Williams, W. L.: Am. J. Obst. & Gynec. **4**:513 (Nov.) 1922.

6. Famulener, L. W.: J. Infect. Dis. **10**:332-368 (May) 1912.

7. Lewis, J. H., and Wells, H. G.: Function of Colostrum, J. A. M. A. **78**:863-865 (March 25) 1922.

globulin content of the serum of three new-born infants after the ingestion of colostrum and found a definite rise in the euglobulin as compared with the serum of one infant that had not been fed with colostrum. From these experiments, Lewis and Wells conclude that colostrum is also of great importance to the human species, since in their opinion, euglobulin is "the predominent protein of colostrum," and "is unique in its association with immune bodies."

Boyd [8] has recently corroborated the findings of Lewis and Wells.

Ten different specimens of cord blood which she analysed were normal as to pseudoglobulin, but showed marked deficiency of euglobulin. Seven infants in these cases showed a definite rise of the euglobulin fraction after the ingestion of colostrum; whereas, the remaining three, who did not receive colostrum, showed a diminished amount of euglobulin.

THE RELATION OF THE STRUCTURE OF THE PLACENTA IN VARIOUS ANIMAL SPECIES TO THE TRANSFERENCE OF IMMUNE SUBSTANCES FROM MOTHER TO OFFSPRING

The studies of Howe on the globulin content of the serums of new-born calves before the ingestion of colostrum, on the one hand, and those of Lewis and Wells, and Boyd, on specimens of human cord blood on the other, show a difference in the permeability of the human and bovine placentas. Thus, in Howe's experiments, the cow's placenta was definitely impermeable to both euglobulin and pseudoglobulin. Lewis and Wells and Boyd agree that the human placenta allows the passage of pseudoglobulin in undiminished quantity, and only euglobulin is held back.

All the evidence cited above seems to indicate that colostrum plays an important rôle in transferring immunity from mother to offspring. These recent experiments are difficult to reconcile with some of the findings of the older investigators who give definite evidence for both placental and milk transmission. Theobald Smith [9] suggested that although he and his co-workers had found that colostrum was of unquestionable importance to the new-born calf, it was his opinion that the same conditions probably did not prevail in other species, and that the factor determining the difference might be found in the structure of the placenta. With this point of view in mind, we sought evidence of histologic differences in the placentas of various species. Grosser [10] who made a comprehensive study of the placenta of different animals has shown that the number of cell layers separating the maternal from the fetal circulation varies according to species, as indicated in Table 1.

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8. Boyd, G. L.: Canad. M. A. J. **12**:724 (Oct.) 1922.
9. Smith, Theobald: Personal Communication.
10. Grosser: Eihäute and Placenta, Vienna and Leipzig, Braumüller, 1909.

The fact that in the human placenta the maternal blood is separated from the fetal by only a single cell layer, whereas, in the case of ruminants, the placenta consists of three cell layers, would seem to indicate a physical basis for the difference in permeability of the bovine and human placentas to globulins as shown by Howe's work on the new-born calf, by that of Lewis and Wells, and by Boyd's on human cord blood. Furthermore, it seemed possible that the differences in the permeability of the placenta in the different animal species, shown by Grosser's chart, might account for some of the discrepancies in the results of various experimenters in the past who have studied the transference of immunity. Thus, some workers claim that the placenta is impermeable to antibodies and that the milk is the only means of transferring immunity to the young. Others insist that

TABLE 1.*—*Variations in Cell Layers Separating Maternal From Fetal Circulation*

Partition Between Maternal and Fetal Blood										
		Maternal (Uterine Mucosa)				Fetal (Chorion)				
Nomenclature		Endothelium	Connective Tissue	Epithelium	Uterus Cavum	Endothelium	Connective Tissue	Epithelium	Types	Remarks
Old	New									
Semiplacentae or Placentae oppositae	Placentae epitheliochorialis	+	+	+	+	..	+	..	Pig	True adeciduate
	Placentae syndesmochorialis	+	+ Partly	— Mostly	—	..	+	..	Ruminants	Transition forms
Placentae verae or Placentae conjugatae	Placentae endotheliochoriolis	+	— Almost entirely	—	—	..	+	..	Carnivora	Placentae zonariae (deciduate)
	Placentae haemochorialis	—	—	—	—	..	+	..	Rodentia, Insectivora, Chiroptera, Apes, Man	Placentae discordales (deciduate)

* Grosser: Eihäute und Placenta, p. 292.

the placenta is permeable and that the placental transmission is the most important mode of transferring antibodies. In analyzing the literature from this point of view, we found a striking conformity of results when cows, horses, goats and sheep were the experimental animals, and a similar correspondence of results when the work was done on human beings, rabbits, guinea-pigs and mice. But there were marked discrepancies between the findings with the former and with the latter groups of animals.

The majority of workers, such as Ehrlich,[11] Merkel,[12] Stäubli,[13] Jurewitsch,[14] Dieudonné,[15] Polano,[16] Schumacher,[17] etc., who worked

11. Ehrlich, P.: Ztschr. f. Hyg. u. Infectionskrankh. **12**:183, 1892.
12. Merkel, H.: München. med. Wchnschr. **8**, 1904.
13. Staübli: Centralbl. f. Bakteriol. **36**:291, 441, 1904.
14. Jurewitsch: Centralbl. f. Bakteriol. **33**:76, 1903.
15. Dieudonné: Cited by Pfaundler.
16. Polano: Ztschr. f. Geburtsh. u. Gynäk. **53**:456, 1904.
17. Schumacher: Ztschr. f. Hyg. u. Infectionskrankh. **37**:323, 1901.

on guinea-pigs, rabbits or man, agreed that the placenta was permeable to antibodies. Roemer,[18] Famulener,[6] Little and Orcutt [1] and others who worked mainly with cows, goats, horses and sheep found the placenta impermeable. Roemer is one of the few investigators who worked with animals of two placental types. In his experiments, the placenta of cows, sheep and horses were uniformly impermeable to antibodies; whereas, with guinea-pigs, rabbits and human beings, he, in practically every instance, found that the antibodies were transmitted through the placenta, though usually in diminished amount.

Bourquin [19] has recently confirmed the permeability of the placentas of guinea-pigs and rabbits to diphtheria antitoxin, hemolysins and agglutinins. An interesting feature of her work is that she examined the placenta in every instance and found no gross lesions.

The conception of the earlier investigators, as represented by the school of Behring, Pfaundler and Roemer, was that the placenta, irrespective of the animal species, was impermeable to proteins and did not permit the passage of maternal antibodies. In their opinion, antibodies only appeared in the fetal blood if the placenta was injured either through disease or by heterologous proteins, such as horse serum antitoxin used in the course of the experiments. Placental transmission of antibodies was, therefore, in their opinion, a pathologic and not a physiologic process.

The opinion that placental injury due to horse serum antitoxin injection determined placental permeability has been conclusively contradicted by a number of workers. They excluded this possibility by immunization of the mother before conception (Stäubli), and by studies on the transference of natural immunity when no injections of any kind were practiced on the mother (Polano). The theory of placental transmission of immune bodies due to injury has, therefore, become untenable.

It seems probable to us that the histologic differences in the structure of the placentas of the various species might sufficiently explain the varying results obtained. In the cases in which the placenta consists of a single layer, as in rodents, apes and man, the greatest degree of permeability has been experimentally observed, and this contrasts strongly with the conditions found among the ruminants. The fallacy of applying facts discovered in one animal species to another is thus indicated.

CONFIRMATION OF THE PERMEABILITY OF THE HUMAN PLACENTA TO DIPHTHERIA ANTITOXIN

In approaching this problem of the permeability of the human placenta to diphtheria antitoxin experimentally, we decided to study

18. Roemer: Beitr. z. exper. Therap. **9**, 1905.
19. Bourquin, H.: Am. J. Physiol. **59**:122 (Feb.) 1922.

the conditions of placental permeability to diphtheria antitoxin in preference to other antibodies because of the ease and accuracy with which this antibody lends itself to quantitative determination.

Historical.—Fischl and Wundscheim[20] were the first investigators to demonstrate diphtheria antitoxin in a large proportion of specimens of cord blood examined by them.

Polano[18] studied the passive transfer of diphtheria antitoxin from mother to child in women who were naturally immune. He was able to demonstrate antitoxin in the cord blood in every case.

Von Groer and Kassowitz[21] made a more extensive study of the same subject. In 84 per cent. of their cases, the cord blood and the maternal blood were identical as to antitoxin content, as titrated by the Roemer method. They conclude that, since they found antitoxin in the cord blood in such a large percentage of cases, the human placenta is normally permeable to diphtheria antitoxin. These investigators found that the Schick reaction did not regularly coincide with the antitoxic content of the maternal serum; but, since they omitted the usual Schick control, their observations cannot be considered conclusive. They made the observation that, in 11.2 per cent. of their cases, when the absence of antitoxin had been demonstrated in the cord blood, they failed to obtain positive Schick reactions in the new-born infant.

Zingher[22] also performed comparative Schick tests, on a series of twenty-three mothers and infants. He found that, with infants under 3 months of age, the Schick reaction in mother and child corresponded in every case except one. Since he did not include any antitoxin determination on the cord bloods and made no Schick tests on infants before they had nursed, it was not clear from his work whether the placenta or the colostrum was the most important agent in transmitting diphtheria antitoxin.

Ruh and McClelland[23] have recently studied a larger series of cases. The infants were all less than 7 days old. Ninety-five mothers and their babies gave corresponding reactions. Seventy-five reactions were negative and twenty positive. In four cases, the mothers gave positive reactions and their babies negative. In only a single instance was a positive reaction obtained in a baby when the mother's reaction was negative. In eight of the cases, Schick tests were performed on infants before they had nursed. Thus the two factors, placental and mammary transmission, could be judged separately. It was found that when the mother gave a negative Schick reaction, the reaction of the infant was negative before the ingestion of colostrum.

Experimental Work.—This included:

1. Determination of the presence of antitoxin in maternal and cord blood by the Kellogg method in mothers giving Schick negative and positive reactions.
2. Comparative Schick reactions in mothers and newly born infants.
3. Determination of any loss of antitoxin by passage through the placenta.

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20. Fischl and Wundscheim: Ztschr. f. Heilk. **16**:429, 1895.
21. Von Groer and Kassowitz: Ztschr. f. Immunität. u. exper. Therap. **23**:108, 1914.
22. Zingher, Abraham: Further Studies in the Schick Test, Arch. Int. Med. **20**:392 (Sept.) 1917.
23. Ruh, H. C., and McClelland, J. E.: Comparison of Diphtheria Immunity in the Mother and in the New-Born, Am. J. Dis. Child. **25**:59 (Jan.) 1923.

Procedure: (*a*) Schick tests were performed on women attending the Sloane Clinic anywhere from one week to three weeks antepartum. At the same time, a specimen of blood was taken. The material for the Schick tests was obtained through the courtesy of the Research Laboratory of the New York City Department of Health. The test was performed according to directions, a control injection of heated toxin being made in every case. Readings on the Schick reaction were made after forty-eight hours, and again after several days.

(*b*) Specimens of cord blood were collected from patients with positive Schick reactions, as well as from those with negative reactions.

(*c*) Comparative determinations for the presence or absence of diphtheria antitoxin in the maternal and the cord blood were made according to the method recently described by Kellogg.[24]

Kellogg's method: Kellogg bases his procedure on the findings of Schick to the effect that a negative Schick reaction indicated at least one-thirtieth antitoxin unit for each cubic centimeter of blood. The L + dose of toxin is diluted in 30 c.c. of saline, so that each cubic centimeter contains one thirtieth of the L + dose. This toxin dilution is then combined with an equal amount of the serum, to be tested and allowed to stand at room temperature for thirty minutes; and 0.2 c.c. is then injected intracutaneously into the shaved skin of a white guinea-pig, this representing one three-hundredth L + dose, together with whatever antitoxin may be contained in 0.1 c.c. of the serum to be tested.

TABLE 2.—*Results of Tests of Maternal and Cord Blood*

Total Number of Cases	Schick Reaction on Mothers		Kellogg Method	
	Positive	Negative	Maternal Blood	Cord Blood
30	11	19	11+*	11+
			19—	19—

* + indicates a positive skin reaction in the guinea-pig, showing less than one-thirtieth antitoxin unit per cubic centimeter of serum tested; — indicates the absence of a reaction in the guinea-pig showing that the serum contained at least one-thirtieth antitoxin unit per cubic centimeter.

Thus, if the patient's serum contains more than one-thirtieth unit of antitoxin for each cubic centimeter, this amount of toxin will be completely neutralized, and no reaction will occur. If the patient's serum contains exactly one-thirtieth unit of antitoxin for each cubic centimeter, it means that one three-hundredth of a minimal lethal dose of diphtheria toxin is left unneutralized, and a slight reddening which never develops into necrosis will occur. If the patient's serum contains less than one-thirtieth unit, reddening and induration, later developing into definite superficial necrosis, result. The readings are best made after from forty-eight to seventy-two hours. Large pigs, weighing from 400 to 500 gm. give the most nearly uniform results.

1. *Determination of the Presence of Antitoxin in Maternal and Cord Blood by the Kellogg Method in Mothers Giving Negative Schick Reactions and in Those Giving Positive Reactions.*—We studied a total of thirty cases in this way. None of the women included in our series gave a history of diphtheria. The results are recorded in Table 2.

Results: Table 2 shows that, in all cases, in which a negative Schick reaction was obtained on the mother, both the maternal serum and the cord blood contained a sufficient amount of antitoxin to give a

24. Kellog, W. H.: A Test for Diphtheria Immunity and Susceptibility, J. A. M. A. **78**:1782-1783 (June 10) 1922.

negative Kellogg reaction on the guinea-pig. In the thirty cases tested by us, we have found that the Schick reaction coincided in every instance with the result obtained by the Kellogg method. In the nineteen mothers giving a negative Schick reaction, we were able to demonstrate the presence of antitoxin in the cord blood in every case. The cord blood obtained from Schick positive cases in no instance contained antitoxin.

2. *Comparative Schick Reactions in Mothers and New-Born Infants.*—We included a series of fifty comparative Schick tests on mothers and infants in our study to see whether we could obtain any information as to the discrepancies reported by previous workers in regard to Schick reactions on the new born. All the infants tested by us were less than 14 days old and were colostrum fed.

Results: The results recorded in Table 3 agree with the findings of others that mothers having Schick negative reactions give birth to

TABLE 3.—*Results in Comparative Schick Tests*

Total Number of Cases	Reactions of Mother and Baby Negative	Reactions of Mother and Baby Positive	Positive Reaction in Mother; Negative or Doubtful Reaction in Baby	Negative Reaction in Mother and Positive in Baby	Pseudoreactions in This Series	
					Mothers	New-born Babies
50	39	4	7	0	10	0

infants having negative reactions, and that the new-born give no pseudoreactions. In Schick positive cases, on the other hand, the reaction in mother and child does not, as noted by previous workers, correspond in every case. In our series a large proportion of the infants born of mothers with positive Schick reaction gave either a negative or an extremely doubtful reaction.

Ruh and McClelland attribute this discrepancy to the peculiar character of the skin of the new-born. They found that greater pressure was required to make an intradermal injection in an infant's skin, and that with the same technic as that used for adults the wheal produced was smaller and disappeared more rapidly.

The difficulties encountered by Ruh and McClelland in performance of the Schick test on infants are in accord with our experience. The failure to obtain positive reactions with regularity in infants is probably due to the fact that the toxin diffuses and is not held within the layers of the skin for a sufficient length of time to obtain a definite local reaction. In order to prove that the failure to obtain a positive Schick reaction was entirely due to the peculiar physical character of the skin of the new-born, we tested the cord blood of six of the seven infants in our series, born of mothers giving

Schick positive reactions and themselves giving a negative or a doubtful reaction, and found a deficiency in antitoxin in every one of these cases when tested by the Kellogg method.

The reactions in the four infants that gave Schick positive reactions were much less definite than those obtained in their respective mothers. The reactions in these new-born infants usually reached their height in twenty-four hours, and the test area then faded rapidly, leaving practically no discoloration except in the colored infants, so that at the end of forty-eight hours the test often appeared negative.

TABLE 4.—*Comparison of Antitoxin Content of Maternal and Cord Blood*

Case	Dilution of L+ Dose in 0.1 C.c.*	Maternal Serum	Cord Blood Serum	Unit per C.c. of Maternal Blood	Unit per C.c. of Cord Blood
1	1/100†	—	—		
	1/50	+	+	1/10†	1/10†
2	1/50	—	—		
	1/25	+	+	1/5	1/5
3	1/50	—	—		
	1/25	+	+	1/5	1/5
4	1/25	—	—		
	1/10	+	+	2/5	2/5
5	1/15	—	—		
	1/10	+	+	2/3	2/3
6	1/50	—	—		
	1/25	+	+	1/5	1/5
7	1/150	—	—		
	1/100	+	+	1/15	1/15
8	1/50	—	—		
	1/25	+	+	1/5	1/5
9	1/50	—	—		
	1/25	+	+	1/5	1/5
10	1/25	—	—		
	1/10	+	+	2/5	2/5
11	1/15	—	—		
	1/10	+	+	2/3	2/3
12	1/150	—	—		
	1/100	+	+	1/15	1/15
13	1/15	—	—		
	1/10	+	+	2/3	2/3

* Actual amount of toxin expressed in fraction of L+ dose.

† Calculations from these measurements were based on the following reasoning: The work of Kellogg, confirmed by us, showed that one three hundredth of the minimal lethal dose of toxin is the smallest amount of toxin that will give a definitely determinable skin reaction, characterized by redness with some induration and subsiding without necrosis. The smallest amount of toxin that will produce a definite necrosis is one fortieth of the minimal lethal dose. Since only Schick negative cases were studied quantitatively, we knew that 0.1 c.c. of all these serums would neutralize at least one three hundredth of the L+ dose. In order to establish the limit of antitoxin content in any particular specimen of blood, a constant amount of serum, 0.1 c.c., was combined with increasing fractions of the L+ dose. The amounts of toxin used in these determinations varied from one one hundred and fiftieth of the L+ dose to one-tenth of the L+ dose. The limits of the neutralizing action of each serum were thus reached, as shown in the chart, the minus sign indicating the largest amount of toxin that gave no reaction at the site of inoculation on the skin of the guinea-pig, and the plus sign a definitely positive skin reaction usually going on to necrosis. The amount of antitoxin per cubic centimeter was thus calculated as follows: In Case 1 in Table 4, 0.1 c.c. of serum plus one one hundredth L+ dose was negative. The serum, therefore, contained one-tenth or more antitoxin units per cubic centimeter, but not much more, since the same amount of the same serum mixed with one-fiftieth L+ dose gave a positive reaction. It, therefore, must have contained more than one-tenth, but less than one-sixth, unit of antitoxin.

From our results, as well as from those obtained by other workers, it seems apparent that the Schick test on the new-born infant is unreliable. The immunity or susceptibility of the new-born infant to diphtheria can therefore be determined with accuracy only by performing a Schick test on the mother or by showing the presence or absence of antitoxin in the cord blood or the infant's blood by the Kellogg method.

3. *Determination of Any Loss of Antitoxin by the Passage Through the Placenta.*—It was the opinion of the older investigators, particularly Roemer, that, even if a certain amount of immune substance did pass through the placenta, the titer of the offspring was always definitely less than that of the mother. It seemed worth while, therefore, to see how the antitoxin content of the maternal and the cord blood compared by accurate titrations according to the Roemer method.

Method: Equal quantities of the serums obtained from the mother's blood and the cord blood were mixed with increasing concentrations of toxin and allowed to stand for thirty minutes at room temperature; 0.2 c.c. amounts were then injected into large white guinea-pigs. Titrations were made until a point was reached at which the antitoxin in the serum failed to neutralize the toxin, and in consequence a skin reaction was obtained, as shown in Table 4. Most of the titrations were repeated several times before a final conclusion was reached.

Results: Table 4 shows that, in the thirteen cases in which the antitoxin content was titrated in maternal and in cord blood, there was no loss of antitoxin by passage through the placenta. Our results agree with those of von Groer and Kassowitz, who also found the titer of antitoxin identical in a large number of specimens of maternal and cord blood.

OBSERVATIONS ON THE RÔLE PLAYED BY COLOSTRUM IN THE TRANSFER OF DIPHTHERIA ANTITOXIN IN HUMAN BEINGS WHEN THE PLACENTA IS KNOWN TO BE PERMEABLE TO ANTITOXIN

In the studies reported above, we have confirmed the observations of a number of other workers in showing conclusively that the human placenta is permeable to diphtheria antitoxin, and it seems likely that this permeability is causally related to the histologic conditions prevalent in human beings, who may be classified on this basis with the placentae verae group.

Colostrum cannot, therefore, be regarded as the sole means of transmission of antitoxic immunity in man. Nevertheless, we believed it important to investigate the possible participation of the colostrum in this process by direct experiment.

1. *Determination of the Presence of Antitoxin in Colostrum of Schick Negative Mothers.*—We attempted to determine the presence of diphtheria antitoxin in the colostrum by means of skin tests, using methods identical with those employed in the case of serum. We found that the control injections of colostrum alone were not readily absorbed and they produced a certain amount of induration which made accurate readings impossible. These irritating effects of the colostrum could be almost entirely eliminated by centrifugalizing, removing the supernatant layer of fat, and corpuscles, and injecting

the clear fluid below. Experiments with this clear fluid were entirely negative. No neutralizing effect was observed with any of the centrifugalized specimens of colostrum tested by us.

The failure to demonstrate antitoxin in the colostrum by the intradermal method seemed to indicate the absence of antitoxin in the colostrum of women giving Schick negative reactions. The studies of previous workers on the antitoxin content of the milk of highly immunized animals showed that the titer of the mammary secretion is always markedly less than that of the blood. It, therefore, seemed possible that antitoxin in human colostrum might be present in very small amounts which could not be readily demonstrated by the intradermal method. We therefore determined to abandon the intradermal method in favor of direct measurements of the protective effect of colostrum by intraperitoneal injection into guinea-pigs.

The only available reports on the antitoxin content of the milk of women naturally immune to diphtheria in which protection tests were employed are those of Pflanz and Schmidt.[25]

They did not examine the colostrum, but studied the milk in six cases during a period of from four to thirty days after delivery. The work of these investigators indicates that the antitoxin content of milk is always from one-tenth to one twenty-fifth less than that of the cord blood, but their experiments do not seem to us reliable, since they used exceedingly small amounts of toxin; namely, 1 minimal lethal dose, combined with relatively large amounts, from 1 to 5 c.c., of milk, mixing the two before injection.

It appeared to us that any method in which milk or colostrum was mixed with toxin before injection might introduce a source of error connected with the possible nonspecific adsorption of toxin by lipoidal and other substances in the milk. Moreover, the employment of simultaneous or of subcutaneous injections appeared fraught with possible error, owing to slow absorption due to the viscid nature of colostrum. For this reason, in order to create conditions most favorable to any possible protective effect on the part of the colostrum or milk, we carried out the experiments by injecting these substances intraperitoneally, twenty-four hours before the toxin was administered. This insured the presence of a maximum number of any protective bodies in the circulation at the time that the dose of toxin was given. All our experiments were controlled by parallel injections of toxin alone. In order to avoid any possibility of nonspecific effects, moreover, the injections of colostrum from women giving negative Schick reactions were in some cases paralleled by intraperitoneal injections of colostrum from women giving Schick positive reactions or of blood serum from Schick positive cases injected into guinea-pigs.

25. Pflanz and Schmidt: Wien. klin. Wchnschr. **42**:955, 1896.

Experimental Work.—It was important in making these estimations to be able to differentiate between colostrum and milk, since we were mainly interested in obtaining information as to the rôle played by colostrum in transferring diphtheria antitoxin. We therefore classified the mammary secretion obtained in the course of our experiments according to the following criteria:

Colostrum: This was defined as the secretion expressed from forty-eight to sixty hours postpartum, which coagulated on boiling and showed the presence of large numbers of colostrum corpuscles under the microscope.

Transitional milk: This was defined as a slightly yellowish secretion obtained from twelve to eighty hours postpartum, which did not coagulate on boiling but still showed a fair number of colostrum corpuscles.

Milk: This was obtained usually on the fourth day postpartum and thereafter. It did not coagulate on boiling and showed none or very few colostrum corpuscles.

Method: Colostrum in quantities ranging from 1 to 8 c.c. obtained from women giving a negative Schick reaction was injected intraperitoneally into guinea-pigs weighing from 250 to 300 gm. At the same time, 1 c.c. of the serum of the cord blood from the same case was also injected intraperitoneally into pigs of similar weight.

In some of our early experiments, control guinea-pigs were injected with colostrum obtained from women giving a positive Schick reaction, but since no protection was ever obtained in this way, this method was abandoned, and the control animals were usually injected with 1 c.c. of serum from a Schick positive case. The toxin was subcutaneously injected, twenty-four hours later. The amount used in our earlier experiments was 1 c.c. of diluted toxin corresponding to one-thirtieth L dose. With this amount, however, the animals lived for as long as from seven to fourteen days. In later experiments, one-fifteenth L + dose was subcutaneously injected in a total volume of 1 c.c., since we found that this amount killed animals weighing from 250 to 300 gm. in from forty-eight to seventy-two hours. When pigs weighing more than 300 gm. were employed, one-tenth L + dose was the amount injected.

In planning the experiments, the heavier pigs were always selected for the colostrum protection experiments in order to throw all the possibility of experimental error on the negative side. Necropsies were performed on all the animals that died, and an experiment was always considered invalid if any pathologic condition other than that due to diphtheria was revealed at necropsy. In the large majority of cases, the typical lesions of diphtheria, enlargement and congestion of the suprarenal glands, edema and necrosis at the point of injection, etc., were found. In a small number of animals, these signs were not typical, but in these, careful necropsy examination revealed no other possible cause of death. All the surviving pigs were kept under observation for at least one month.

By this method, we examined twenty specimens of colostrum. The results of these examinations are detailed in Tables 5 and 6.

Results: The results presented in Table 5 may be summarized thus: In nine of the cases reported, 1 c.c. of the serum obtained from the cord blood protected completely against the amount of toxin used, while in all but one of these cases the colostrum was entirely ineffective even with the largest amount used. In Case 4, the pig injected with

TABLE 5.—*Results of Protection Tests with Colostrum and Cord Blood*

	Colostrum						Cord Blood					Controls			
Case	Hours Post-partum	Amount Injected Intraperitoneally, C.c.	Pig	Weight, Gm.	1 C.c. Toxin Subcutaneously	Result	Amount Injected Intraperitoneally, C.c.	Pig	Weight, Gm.	1 C.c. Toxin Subcutaneously	Result	Pig	Weight, Gm.	1 C.c. Toxin Subcutaneously	Result
1	48	2	A591	275	1/15 L+	Death, 48 hrs.	1	A588	250	1/15 L+	Discharged	A598	275	1/15 L+	Death, 48 hrs.
	48	6	A590	275	1/15 L+	Death, 48 hrs.									
2	48	2	A677	280	1/15 L+	Death, 72 hrs.	1	A675	230	1/15 L+	Discharged	A688	240	1/15 L+	Death, 72 hrs.
3	48	1	A499	275	1/15 L+	Death, 48 hrs.	1	A535	230	1/15 L+	Discharged	A689	240	1/15 L+	Death, 72 hrs.
	48	3	A686	270	1/15 L+	Death, 72 hrs.									
4	48	1	694	315	1/10 L+	Death, 96 hrs.	1	692	285	1/15 L+	Discharged	685	295	1/10 L+	Death, 48 hrs.
	48	4	499	305	1/10 L+	Discharged									
5	70	1	677	315	1/10 L+	Death, 48 hrs.	1	680	275	1/10 L+	Death, 96 hrs.	686	295	1/10 L+	Death, 48 hrs.
	70	4	687	310	1/10 L+										
6	66	2	186	275	1/15 L+	Death, 72 hrs.	1	691	240	1/15 L+	Discharged	675	245	1/15 L+	Death, 72 hrs.
	66	2	695	250	1/15 L+										
7	53	8	529	375	1/10 L+	Death, 72 hrs.	1	526	325	1/10 L+	Discharged	A535	335	1/10 L+	Death, 72 hrs.
8	57	4	692	245	1/15 L+	Death, 72 hrs.	1	676	235	1/15 L+	Death, 10 days	693	240	1/15 L+	Death, 48 hrs.
9	48	4	682	265	1/15 L+	Death, 72 hrs.	1	681	255	1/15 L+	Discharged	697	260	1/15 L+	Death, 48 hrs.
10	56	6	A191	290	1/15 L+	Death, 96 hrs.	1	A186	275	1/15 L+	Death, 8 days	281	280	1/15 L+	Death, 72 hrs.
11	48	4	535	305	1/10 L+	Death, 72 hrs.	1	532	285	1/15 L+	Discharged	538	295	1/10 L+	Death, 48 hrs.
												522	275	1/10 L+	
12	24	2	307	260	1/30 L+	Death, 5 days	1	A465	260	1/20 L+	Discharged	282	260	1/30 L+	Death, 7 days
	24	5	158	255	1/30 L+	Death, 72 hrs.						A468	255	1/30 L+	Death, 15 days

TABLE 6.—*Results of Protection Tests with Colostrum and Cord Blood*

	Colostrum						Cord Blood					Controls			
Case	Hours Post-partum	Amount Injected Intraperitoneally, C.c.	Pig	Weight, Gm.	1 C.c. Toxin Subcutaneously	Result	Amount Injected Intraperitoneally, C.c.	Pig	Weight, Gm.	1 C.c. Toxin Subcutaneously	Result	Pig	Weight, Gm.	1 C.c. Toxin Subcutaneously	Result
1	65	5	689	280	1/15 L+	Discharged	1	A512	240	1/15 L+	Discharged	688	275	1/15 L+	Death, 72 hrs.
2	33	4	A523	280	1/15 L+	Discharged	1	A528	275	1/15 L+	Discharged	281	280	1/15 L+	Death, 72 hrs.
3	44	5	A527	275	1/15 L+	Discharged	1	A531	260	1/15 L+	Discharged	524	270	1/15 L+	Death, 72 hrs.
4	37	5	A166	375	1/15 L+	Discharged	1	A596	205	1/15 L+	Discharged	500	280	1/15 L+	Death, 96 hrs.
	37	5	A191	245	1/15 L+	Discharged									
5	60	7½	534	305	1/10 L+	Discharged	1	521	270	1/10 L+	Discharged	538	295	1/10 L+	Death, 48 hrs.
6	41	6	A497	280	1/15 L+	Discharged	1	A500	195	1/15 L+	Discharged	A499	255	1/15 L+	Death, 48 hrs.
7	32	5½	A166	275	1/15 L+	Death, 7th day	1	A484	250	1/15 L+	Discharged	A317	265	1/15 L+	Death, 48 hrs.
												A596	250	1/15 L+	
8	30	6	A481	300	1/15 L+	Discharged	1	226	235	1/15 L+	Discharged	255	270	1/15 L+	Death, 48 hrs.
	53	7½	A171	215	1/15 L+							235	260	1/15 L+	
	53	6½	A480	235	1/15 L+										

TABLE 7.—*Results of Protection Tests with Transitional Milk and Cord Blood*

	Transitional Milk						Cord Blood					Controls			
Case	Hours Post-partum	Amount Injected Intraperitoneally, C.c.	Pig	Weight, Gm.	1 C.c. Toxin Subcutaneously	Result	Amount Injected Intraperitoneally, C.c.	Pig	Weight, Gm.	1 C.c. Toxin Subcutaneously	Result	Pig	Weight, Gm.	1 C.c. Toxin Subcutaneously	Result
1	60	7	A635	220	1/15 L+	Death, 72 hrs.	1	219	210	1/15 L+	Discharged	A507	230	1/15 L+	Death, 48 hrs.
	60	5	A487	245	1/15 L+							255	290	1/15 L+	
	60	5	225	225	1/15 L+										
2	80	8	A496	275	1/15 L+	Death, 48 hrs.	2	235	195	1/15 L+	Discharged	A429	255	1/15 L+	Death, 48 hrs.
												A498	215	1/15	Death, 24 hrs.
3	72	2	A587	275	1/15 L+	Death, 72 hrs.	1	A635	250	1/15 L+	Discharged	A592	300	1/15 L+	Death, 73 hrs.
	72	2	A634	275	1/15 L+										

1 c.c. of colostrum died; whereas, the one that had received 4 c.c. survived, indicating that in this instance a certain amount of antitoxin was present in the colostrum. In the three remaining cases, 1 c.c. of the serum did not give complete protection, but in all of them death was delayed in the pigs given serum injections, longer than in those that had received colostrum. The concise fact apparent from these twelve cases is that the antitoxin content of the colostrum is less than that found in the cord blood of the same case.

The fact that, in the measurements described in Table 5, a certain amount of protective action was observed when sufficient amounts of colostrum were used encouraged us to continue with series in which we employed the largest amounts of colostrum available, instead of attempting to divide the colostrum into various samples and to make quantitative estimates. The series in Table 6 represents an experiment in which the amounts of colostrum were never less than 4 c.c., and as high as 7.5 c.c. in individual cases.

Results: In this series of eight cases, as presented in Table 6, the cord blood in amounts of 1 c.c. protected with regularity, as did the colostrum of the same cases in quantities ranging from 4 to 7.5 c.c. In one case, only, in which 5.5 c.c. of the colostrum had been injected, the guinea-pig died after seven days. The experiment thus shows definitely that antitoxin may be contained in the colostrum, and, taken together with the results in Table 5, it would seem to indicate that the antitoxin content of the colostrum is regularly less than that of the cord blood. Nevertheless, we realize that the experiment outlined in Table 6 is defective to this extent: we have no means of quantitatively estimating or comparing the antitoxin content of serum and of colostrum, except in Case 7. This defect was unavoidable because, owing to our desire to waste none of the colostrum, we injected the largest available amount into the pig in each case. However, there seems little reason seriously to question the relatively larger antitoxin content of the cord blood.

The methods used in the foregoing experiments with colostrum were applied without change of principle in the following experiments, in which we investigated the antitoxin content of milk and transitional milk. The only difference in these cases was that we used considerably larger quantities of the milk. In the case of the transitional milk, the amounts were similar to those used in the case of colostrum.

The experiments summarized in Tables 7 and 8, then, show that we were able to find no protective, and therefore no antitoxic, properties either in transitional milk, or in milk, in spite of the fact that in a number of cases investigated a certain amount of protective effect had been manifested during the colostrum stage.

Evidence That the Antitoxic Titer of Infants' Serum After the Ingestion of Antitoxin-Containing Colostrum is Not Raised Above That in the Cord Blood.—Blood was obtained from the infants in five of the cases in which the colostrum had given definite evidence of containing antitoxin (Table 6). The children were bled at intervals of from six to ten days after birth, and the serum was collected after clotting. The antitoxin contents of this serum was them determined by the Roemer method and compared in parallel experiments with serum previously obtained from the cord blood of the same case.

TABLE 8.—*Results of Protection Tests with Milk*

	Milk						Controls			
Cases	Days Post-partum	Amount Injected I. P. C.c.	Pig	Weight	1 C.c. Toxin Subcut.	Result: Death in	Pig	Weight	1 C.c. Toxin Subcut.	Result: Death, Hours
1	12	8	A492	365	1/10 L+	48 hours	535	335	1/10 L+	48
2	10	7	A536	260	1/15 L+	72 hours	A524	270	1/15 L+	72
3	11	10	A496	220	1/15 L+	48 hours	500	280	1/15 L+	96
4	4	6	A495	210	1/15 L+	72 hours	A317	265	1/15 L+	48
5	10	8	A507	345	1/10 L+	72 hours	440	315	1/10 L+	48
							258	230	1/10 L+	
6	4	8	A522	370	1/10 L+	72 hours	A535	335	1/10 L+	48
7	4	8	499	325	1/15 L+	72 hours	281	280	1/15 L+	72
8	4½	6	A166	220	1/15 L+	48 hours	255	220	1/15 L+	48
	4½	6	A440	220	1/15 L+		571	290	1/15 L+	72
9	12	10	A499	220	1/15 L+	5 days	500	250	1/15 L+	96

TABLE 9.—*Results of Tests of Infants' Serum from Six to Ten Days After Birth*

Case	Toxin Dose in 0.1 C.c.	Serum from Cord Bloods 0.1 C.c.	Infants' Serums 0.1 C.c.	Unit of Antitoxin per C.c. of Cord Blood	Unit of Antitoxin per C.c. of Infant's Blood
1	1/50 L+	—	—		
	1/25 L+	+	+	1/5	1/5
2	1/5 L+	—	—	2 units or more	2 units or more
3	1/25 L+	—	—	2/5 or more	2/5 or more
4*	1/50 L+	—	—		
	1/25 L+	—	+	2/5	1.5
5	1/50 L+	—	—		
	1/25 L+	+	+	1/5	1/5

* Titrations repeated three times.

Result: Table 9 shows that in none of the cases examined did the serum of the infant taken from six to ten days after birth, after ingestion of all the colostrum which the mother could furnish, show any increase of antitoxin content over that of the original cord blood. In Cases 2 and 3, there was too little serum available to complete the titrations. But as far as they could be carried out they showed no difference between the cord blood and the serum of the infant. In one case, in which three separate titrations were made, the titer of the infant's blood was regularly lower than that of the cord blood.

Identical results were obtained in seven other cases, as shown in Table 10. In these cases, the mothers all gave Schick negative reactions, but we had no opportunity to examine the antitoxin content of the colostrum of these women.

CLINICAL INQUIRY INTO THE IMPORTANCE OF COLOSTRUM TO THE NEW-BORN INFANT

As stated in our introduction, the work recorded in this paper was undertaken largely as a result of the investigations of Theobald Smith and his co-workers on calves. His investigations seem to indicate that, in these animals, colostrum was not only important, but could be regarded almost as essential to survival, a majority of the animals that never received colostrum dying during the first week of life of a

TABLE 10.—*Results of Tests of Infants' Serum*

Case	Toxin Dose in 0.1 C.c.	Serum from Cord Bloods 0.1 C.c.	Infants' Serums 0.1 C.c.	Unit of Antitoxin per C.c. of Cord Blood	Unit of Antitoxin per C.c. of Infant's Blood
1	1/50 L+	—	—		
	1/25 L+	+	+	1/5	1/5
2	1/100 L+	—	—		
	1/50 L+	+	+	1/10	1/10
3	1/15 L+	—	—		
	1/10 L+	+	+	2/3	2/3
4	1/50 L+	—	—		
	1/25 L+	+	+	1/5	1/5
5	1/50 L+	—	—		
	1/25 L+	—	+	2/5	1/5
6	1/15 L+	—	—		
	1/10 L+	+	+	2/3	2/3
7	1/15 L+	—	—		
	1/10 L+	+	+	2/3	2/3

Bacillus coli infection, spoken of as scours. Although it was quite apparent to Theobald Smith that no sweeping application of these observations to conditions prevalent in human beings could be made, it, nevertheless, seemed of considerable importance to investigate this question experimentally.

Essential to a proper understanding of the conditions in man was a determination of the relative importance of the transmission of antibodies from mother to infant through the placenta or through colostrum and milk. This was particularly important in view of Smith's conclusion that the value of the colostrum in calves depended largely on the transmission of antibodies. In carrying out these studies, we should have liked to include investigation into the transmission of agglutinins and other antibodies, as well as into these conditions as applied to antitoxins, which, after all, are physically and chemically quite distinct from other protective substances in serum. A lack of suitable material prevented this. We, therefore, believed it best to

restrict ourselves to an accurate study of an antibody that could be measured with precision, and for this reason studied the transmission of antitoxin.

Although such studies seemed to us of distinct value, they have little meaning from the purely clinical point of view unless they are

TABLE 11.—*Clinical Records of New-Born Infants Who Never Obtained Colostrum* *

Case	Days in Hospital	Birth Weight Lbs.	Birth Weight Oz.	Weight on Discharge Lbs.	Weight on Discharge Oz.	Feedings	Remarks	Cause of Death of Mother
1	31	4	12	4	7	6:20 formula	Child thin; in need of special care	Hemorrhage
2	120	4	1	10	..	Modified formula	Always did well.....	Eclampsia
3	44	3	15	5	7	Powdered milk	Premature; developed pustules, which cleared on the 15th day	Eclampsia
4	20	6	13	6	14	8:20 formula	Initial loss, 8 oz.; then gained until discharge	Bronchopneumonia
5	45	5	3	6	3	8:20 formula	No fluctuation; child in good condition	?
6	7	2	6	2	4	Modified formula	Birth premature; temperature always subnormal; death on 7th day	?
7	20	6	2	6	8	6:20 formula	Developed abscesses from 10th day on, but all cleared; stools remained normal; temperature normal; gained in weight	Toxemia of pregnancy; hemorrhage
8	78	3	14	6	9	6:20 formula	Premature; developed eye discharge; which cleared up; temperature normal	Toxemia
9	23	8	2	8	4	Powdered milk	Gained 7 oz. from 21st to 23d day	Bronchopneumonia
10	14	5	12	5	2	Modified formula	Initial loss, 14 oz.; then started to gain	Eclampsia
11	6	6	2	6	6	Powdered milk	Practically no initial loss; temperature normal	Eclampsia
12	45	6	10	7	14	Formula alternated with breast milk	Stools green, with curds, gradually becoming normal; after 30 days, developed abscesses on abdomen, which cleared in a week	Eclampsia
13	7	6	2	6	7	Powdered milk	No initial loss.....	Eclampsia; cesarean delivery
14	13	4	12	3	11	Breast milk	Premature; cyanotic; hemorrhagic disease of new-born; received fluids, transfusions; died	Eclampsia during delivery
15	16	7	..	6	13	Modified formula	Initial loss, 10 oz.; then progressively gained 8 oz.	Eclampsia; lived
16	32	5	3	6	0	Modified formula	Premature; temperature normal; stools normal	Eclampsia
17	7	8	9	7	12	Modified formula	Took food well; started to gain	Hemorrhage
18	7	?	?	8	2	Condensed milk, then breast milk	Brought to hospital after delivery because of hemorrhage of mother; put on condensed milk, then to breast after colostrum had been withdrawn	Mother lived

* From the files of Sloane Maternity Hospital, New York Nursery and Child's Hospital and Manhattan Maternity Hospital for the last three years, 1919-1922.

combined with an inquiry into the degree to which colostrum actually contributes to the health of the new-born child; for the point of departure of Theobold Smith's investigations was the clinical observation of this essential rôle played by colostrum in the survival of calves.

Although it is not easy to obtain such records in human beings, we believed it distinctly worth while to make an extensive search of available records of hospitals accessible to us. By searching the files of the Sloane Hospital for Women, the New York Nursery and Child's Hospital and the Manhattan Maternity Hospital, we succeeded in finding eighteen cases in which the records were sufficiently complete to seem to us to offer valid material for information on this question. We studied the records of the hospitals named over a period of three years, from 1919 to 1922. The evidence in no case was considered sufficiently reliable for our purposes unless the mother had died during delivery, or within the first twenty-four hours after delivery, and unless there was unquestionable evidence in the record that the infant had never been put to the breast. It is not surprising that rigid adherence to such rules resulted in a relatively small yield of available cases. In two cases only were these rules relaxed, and in these the entire clinical course was under our direct control, and we were able to assure ourselves by personal observation that colostrum was never ingested.

In Table 11, we summarize the facts that seem to us essential to a proper appraisal of these eighteen cases.

Results: As far as any conclusion can be drawn from a clinical series as small as the one recorded in Table 11, it would seem that we were justified in assuming that no serious harm attributable to lack of colostrum accrues to the new-born child. The clinical records of these children differ in no way from the average clinical course of colostrum-fed infants. In no case did the records show diarrhea, septic infection, or any of the symptoms of disease analogous to that which seems to occur with such regularity in calves deprived of colostrum. In only Cases 6 and 14 did the children die, on the seventh and thirteenth day after birth, respectively. Both were premature, the first weighing only 2 pounds and 6 ounces (1,077 gm.), a weight which is generally regarded as incompatible with life; the other case was recognized as an unmistakable instance of hemorrhagic disease of the new-born. Three other infants were premature (Cases 3, 8 and 16), and these did well, indicating that even prematurely born children may thrive without the aid of colostrum. It seems of further importance that all of the children in the series were born of mothers who died of severe toxemia, bronchopneumonia or hemorrhage, and in many instances death occurred during labor. These facts, if of any weight at all, are additional evidence in favor of the nonessential nature of the colostrum, since all of these children started under unfavorable conditions.

COMMENT

The studies here reported were undertaken largely because of the possibly important bearing on infant feeding of the work of Theobald

Smith and his collaborators on the essential nature of colostrum feeding in calves. Smith's observations were limited, both in experiment and conclusions, to calves, and no suggestion was made by him that similar conditions might prevail in human beings. Indeed, in our first consultation with him, he suggested probably fundamental anatomic and physiologic differences which should prevent loose generalization in the application of his results to other species. In spite of this fact, his paper was followed by a number of editorial and other articles in the medical press in which such generalizations were made, and in which the observations of Theobald Smith and his pupils were regarded as directly applicable to man. It seemed essential, therefore, that the problem as applied to human beings be made the subject of direct experiment.

In attempting to explain the reason for the protective effect of colostrum in calves, Theobald Smith suggested the possibility that colon bacillus infection, which is etiologically basic to the disease known as scours, might be arrested or prevented by antibodies conveyed to the calves in colostrum. This suggestion was largely based upon the observations of Little and Orcutt, assistants of Theobald Smith, to the effect that the blood of new-born calves did not contain agglutinins against *Bacillus abortus* until after the intake of agglutinin-containing colostrum. Howe, furthermore, showed that the globulin fractions of the proteins which are usually associated with antibodies are lacking in the new-born until after the calves have ingested colostrum, which contains these globulins.

These observations on calves suggested to us that the most direct approach to the problem in human beings lay along two separate lines of investigation: (1) the determination of the manner in which antibodies are conveyed from mother to child, comparing antibody contents of colostrum with those of the blood of the mother, the cord blood and the blood of the infant, after the ingestion of colostrum, and (2) by a clinical study of any reliable records of noncolostrum-fed infants that we could find.

On some phases of this problem, a considerable amount of work has been done in the past. We refer, particularly, to the work of Famulener, published in 1912. Famulener studied the transmission of hemolysins from actively immunized goats to their kids, during the course of pregnancy. The gist of Famulener's studies, which have been mentioned in our introduction, was that these antibodies were transmitted chiefly by the colostrum, but it is worth mentioning that he obtained transmission only in cases in which the mother goat had been immunized to a considerable degree, and possessed a relatively high concentration of hemolytic antibodies.

In view of Theobald Smith's observations, we would have preferred to carry out our work by studying the transmission of agglutinating antibodies, since this would have had more direct bearing on preceding investigations. But, failing, after investigation at a number of large hospitals, to find cases in which agglutinins, either for typhoid or colon bacilli, were present in sufficient concentration in the mother to make the inquiry of value, we finally restricted our study to the transmission of diphtheria antitoxin, since this substance is frequently present in accurately measurable quantities in human beings, and since it lends itself to precise quantitative determination by a variety of methods applicable to conditions such as those investigated by us.

The literature of past investigations into the transmission of antitoxin presents many contradictions. In studying these, it became apparent to us that these contradictions might easily be explained by the fact that various investigators had worked with animals of different species, and a study of the histologic structure of the placentas of the various species employed, as tabulated in the work of Grosser, revealed an astonishing coincidence of placental transmission with relative histologic simplicity of placental structure. Thus, positive placental transmission was generally found in the species grouped as possessing a placenta vera, in which only one cellular layer intervenes between maternal and fetal blood; while in researches in which no placental transmission was revealed, the animals studied generally belonged to species in which the placental structure was considerably more complex.

It is interesting to note, at this point, some of the striking differences in the conditions of mammary secretion in animals, such as cows, with the placenta impermeable, and the new-born calf dependent mainly on the colostrum for the transmission of antibodies; and in man, with the placental structure simpler and more permeable. The cow's udder at the time of parturition is filled with approximately 20 pounds of colostrum, which is immediately and reflexly ingested by the calf shortly after birth to the extent of about two pounds at the first feeding. In human beings, colostrum does not appear for at least twelve hours after birth and is secreted in amounts not greater than 5 c.c. in the first twenty-four hours after birth, and not exceeding 90 c.c. after forty-eight hours; and in this case nursing of the child is not spontaneous but must be stimulated.

CONCLUSIONS

1. A striking difference exists in regard to the passage of antibodies through the placenta in various species of animals, as shown by a review of the literature. In goats and cows, with a placental structure fairly complex, placental transmission of immune substances does not occur, and the colostrum is the main agent for transmitting

immunity from mother to offspring. In rodents and man, with a placental structure relatively simple, placental transmission of immune substances has been demonstrated by many different observers.

2. In accordance with the results of previous workers, we have found that the human placenta is permeable to diphtheria antitoxin.

3. In mothers giving a negative Schick reaction, both the maternal and the cord blood contain at least one-thirtieth unit of diphtheria antitoxin per cubic centimeter, as determined by the Kellogg method. In mothers giving a positive Schick reaction, both the maternal and the cord blood contain less than one-thirtieth unit of diphtheria antitoxin per cubic centimeter, as determined by the Kellogg method.

4. Comparative Schick reactions on mothers and infants show that mothers giving negative Schick reactions give birth to infants giving negative reactions.

5. Infants born of mothers giving Schick positive reactions fail, in a certain percentage of cases, when the cord blood has been shown to be deficient in antitoxin, to give a positive Schick reaction. This depends probably on technical difficulties coincident to intracutaneous injections in new-born infants. A Schick negative reaction in a new-born infant cannot, therefore, with certainty be interpreted as meaning that the infant is immune to diphtheria. Hence, we suggest that, if the susceptibility of very young infants to diphtheria is to be determined, the Schick test can most easily and reliably be performed on the mothers, since the placental transmission of diphtheria antitoxin has been conclusively proved.

6. The concentration of antitoxin in the cord blood corresponds with considerable accuracy to that in the blood of the mothers, there being no measurable loss of antitoxin in passage through the placenta.

7. Human colostrum occasionally contains small amounts of antitoxin, but this amount is always less per volume than that found in the blood serum of the mother or in the cord blood.

8. Transitional milk and milk, in our investigations, never showed the presence of antitoxin.

9. The antitoxin content of the infant's blood in none of our cases showed an increase attributable to colostrum feeding.

10. Careful clinical study of eighteen cases in which there was no possibility of error concerning the ingestion of colostrum revealed no evidence of any possible harm to the infant due to the omission of colostrum.

11. As far as our investigations go, they indicate that colostrum feeding in human beings has no significance whatever comparable to that revealed by the work of Theobald Smith and his co-workers in the feeding of the newborn calf.

A CASE OF CEREBRAL CYST IN AN INFANT*

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Cysts of the brain are of infrequent occurrence, and their detection clinically is extremely difficult. In the majority of cases, the condition is diagnosed only by postmortem examination. The case reported herewith presented several interesting features, briefly: (1) the sudden onset of symptoms simulating an acute infectious process; (2) indefinite signs and symptoms, making an antemortem diagnosis impossible, and (3) the presence of hyperglycemia and glycosuria.

In reviewing the literature, it is of interest to note that Starr,[1] who collected 299 cases of brain tumors in children, found that thirty of these, or nearly 10 per cent., were cysts. The locations were: basal ganglion and lateral ventricle, 1; pons, 1; medulla, 1; base, 1; cerebellum, 9, and centrum ovale, 15. Two of the tumors were multiple. Several interesting cases have been reported, occurring in adults. Anglade[2] reported a case of hydatid cyst of the brain. His patient, a woman, aged 44 years, was afflicted with epileptiform seizures and hemiparesis of the left side, dulling of the intellect, dysarthria and an intention tremor. The cyst was located beneath the posterior horn of the lateral ventricle of the left side and measured about 6 cm. in the long axis and 4 cm. in width. Ross[3] reported a case in a woman, aged 55 years, who had mental symptoms, hemiparesis on the left side, cerebellar ataxia and an intention tremor. Here the cyst was situated in the anterior part of the third ventricle, arising as a simple retention cyst from the connective tissue of the velum interpositum. Lambert,[4] Hoppe,[5] Hunt,[6] and Remsen[7] have reported similar cases.

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* Received for publication, April 19, 1923.

* From the Jacobi Division for Children, Lenox Hill Hospital, Dr. A. L. Goodman, Director.

1. Starr, M. A.: Organic and Functional Nervous Diseases, Ed. 4, Philadelphia, Lea & Febiger, 1913.

2. Anglade, D.: Hydatid Cyst in Brain, J. de méd. de Bordeaux **92**:119-121 (March 10) 1921.

3. Ross, D. M.: Notes on a Case of Cyst in the Third Ventricle, J. Ment. Sc., London **63**:252-257, 1917.

4. Lambert, A. V. S.: Cyst of the Interpeduncular Space, Neurological Bull. **2**:53 (Feb.) 1919.

5. Hoppe, H. H.: A Report of Seven Operations for Brain Tumors and Cysts, J. A. M. A. **36**:302 (Feb. 2) 1901.

6. Hunt, J. R.: Congenital Cysts of the Fourth Ventricle, Am. J. M. Sc., March, 1904.

7. Remsen, C. M.: Operative Intervention in Cysts of the Left Cerebral Hemisphere, etc., J. A. M. A. **63**:1649 (Nov. 7) 1914.

REPORT OF CASE

History.—A boy, aged 1 year, admitted, Oct. 28, 1922, with the complaint of vomiting and drowsiness of one day's duration, had a negative personal history except for the fact that, three weeks prior to admission, he had had several attacks of vomiting, extending over a period of two days. These occurred without any regularity or relation to the intake of food, were not projectile and ceased on the next day. The family history revealed that the first child had died at an early age from an unknown cause. The second child was living and well. The father was definitely tuberculous.

The patient had vomited twice on the morning previous to admission, and had appeared drowsy and out of sorts. On the day of admission, he was semicomatose. He had a good bowel movement that morning, and in addition an enema had been given, with good results. The appetite was poor. The infant was extremely restless and its sleep had been interrupted by sharp sudden outcries. Occasionally, convulsive movements were noticed, during which the head was thrown back, the abdomen arched forward and the extremities extended.

Examination.—The infant was in a comatose state, breathing rather heavily. The entire body was completely relaxed and felt cold. The pulse was 82 per minute and irregular both in rate and in force. The temperature was 95.6 F. The respirations were 40. There was a bilateral ptosis present, and both pupils were dilated and failed to respond to light. The corneal reflex, however, was still present, and the eyegrounds were negative. The ears and nose were negative. The tongue was coated and protruded from between the lips, which were dry. The other positive findings were: signs of beginning pulmonary edema; weak and irregular heart sounds; distended bladder; exaggerated knee-jerks and the presence of a Babinski reflex. There was no ankle clonus or Kernig reaction.

Laboratory Findings.—The white blood cells numbered 25,000; polymorphonuclears, 82 per cent.; lymphocytes, 18 per cent. Lumbar puncture showed the spinal fluid to be under normal pressure and clear, with a cell count of 900, of which 78 per cent. were lymphocytes and 22 per cent. polymorphonuclears. Culture of the fluid was sterile. The globulin reaction was markedly positive.

Chemical analysis of the blood showed a creatinin content of 0.7 mg. per hundred cubic centimeters of blood, and a sugar content of 175 mg. The urine, which was straw colored, on admission showed a specific gravity of 1.011. It contained no albumin, but showed a considerable amount of reducing substance. The following day, a second examination revealed albumin and 0.8 per cent. of sugar. The sediment contained several groups of epithelial cells and many bacteria.

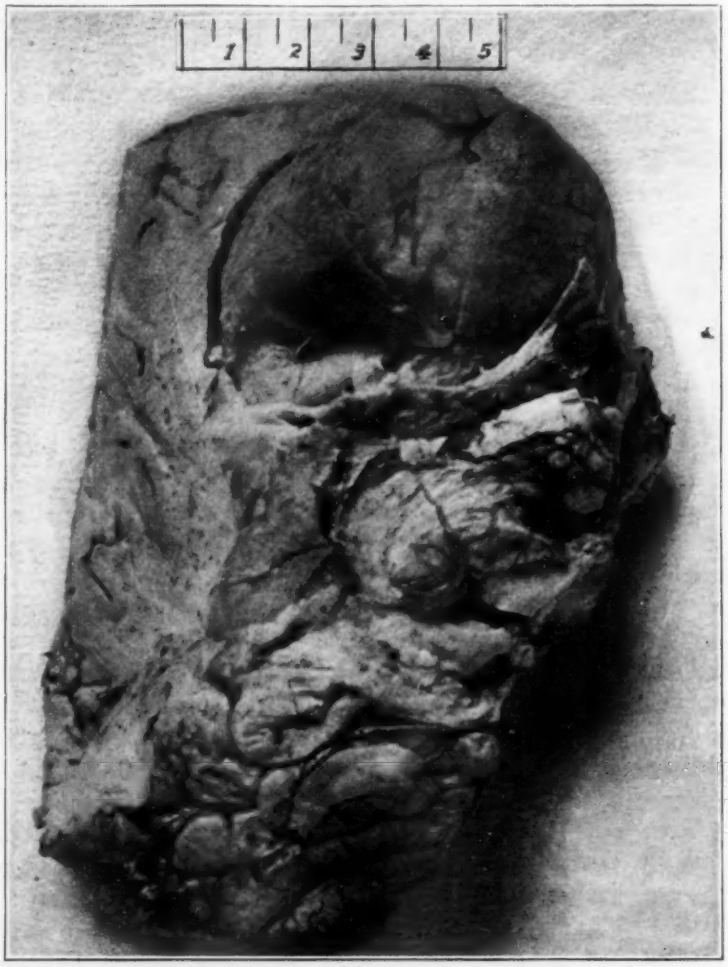
Clinical Course.—The patient continued in a comatose state, with the temperature gradually rising until it reached 105 F., the following evening. The pulse became more rapid and irregular. The edema of the lungs became more marked, and death occurred from respiratory failure, about thirty hours after admission.

Necropsy Findings.—Skull: When the calvarium was opened an excessive amount of cerebrospinal fluid escaped. The convolutions were markedly flattened, more so over the right than over the left hemisphere. There was a marked edema involving the pia of the brain. When the lateral ventricles were opened, they were found to be considerably distended. Beneath the posterior horn of the lateral ventricle of the right side, and separated from the ventricle by 0.2 mm. of brain tissue, was a fluctuating cyst, on the surface of which were numerous newly formed blood vessels of fair diameter. The cyst distorted the lenticular nucleus and was not adherent to the brain tissue, from which it could be shelled out. The outer surface of the brain in the posterior convolutions covered the cyst to a thickness of 0.3 cm. The cyst wall was thin, dense and white. It contained 60 c.c. of a creamy yellowish fluid, the chemical

analysis of which will be given later. Its cellular content consisted of a large number of lymphocytes, which were undergoing fatty degeneration.

Lungs: Both lungs showed, in their posterior and inferior aspects, a diffuse edema, without areas of consolidation.

The liver, pancreas, gallbladder, suprarenals, bladder, ureters, kidneys, gastro-intestinal tract and spleen were normal. The lymph glands of the



Section of right cerebral hemisphere showing cyst, posteriorly situated, with lateral ventricle removed.

mesentery of both the large and the small intestine were enlarged, measuring from 0.04 to 1.2 cm. in diameter, and were pink. There was a secondary paralytic ileus involving the last half of the small and the first half of the large intestine.

Microscopic Examination.—The mesenteric glands showed a partially healed tuberculous process. The cyst wall was composed of dense, laminated connective tissue, richly infiltrated with round cells and having adherent to its inner surface a fair number of polymorphonuclear leukocytes.

The contents of the cyst consisted of a cloudy greenish fluid, colloid in nature, which, on chemical examination, proved to be insoluble in water and acetic acid but was dissolved by dilute potassium hydroxid. The principal constituent was pseudomucin, which yielded a carbohydrate (glucosamin). The specific gravity was 1.029; total nitrogen, 1.3 gm.; total protein (Purdy method), 2.78 gm.; uric acid, 5.5 mg. per hundred cubic centimeters; creatinin, 0.085 mg.; potassium, 0.04 mg.; calcium, 0.0116 mg.; sodium, 0.162 mg.; chlorids as sodium chlorid, 0.360 per cent., and cholesterol, 200 mg. per hundred cubic centimeters. This type of cyst, according to Hammersten,[8] may be considered of the proliferative type, the characteristic constituents of which are metalbumin and paralbumin.

COMMENT

Clinical Data.—This report shows how confusing the clinical picture may be in cerebral conditions of infants, especially when no localizing signs can be elicited. One has to depend usually on objective findings, such as the presence of pathologic reflexes, to be able to arrive at a diagnosis. Even these are often misleading. The presence of a Babinski reflex is without significance at this age.

While a carefully taken history may sometimes lead one to suspect the presence of such a condition, we must remember that various disorders of infancy may set in with fever, vomiting and convulsive seizures.

The presence of hyperglycemia and glycosuria in this case is of interest. It is rather difficult to say whether they may be regarded as features of a terminal condition, or whether pressure of the cyst on the fourth ventricle stimulated the so-called carbohydrate center, simulating the puncture diabetes of Claude Bernard,[9] who found that injury to the floor of the fourth ventricle in dogs and rabbits produced, almost invariably, a discharge of sugar in the urine. This was known as the sugar puncture. The glycosuria was only temporary and never had a fatal ending. It was found, on further investigation, that the puncture produced glycosuria only when the animals had been fed on carbohydrates or were well fed. Starving animals produced little or no sugar.

What the actual cause of death was in this case it would be difficult to state. It seems likely that there occurred a sudden distention of the cyst, with increasing pressure upon the vital centers.

Pathology.—The formation of cysts in the brain has been attributed to a variety of causes. Bruns, while admitting that the etiology of such cysts remains largely in doubt, offers the following classification: (1) those of congenital origin; (2) parasitic; (3) traumatic; (4) those resulting from brain softening, and (5) those without any accountable etiology. Various other classifications have been made, none of which seem to cover the field completely.

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8. Hammersten and Hedin: Physiological Chemistry, pp. 624-627, 1915.
9. Bernard, Claude: Leçons sur la diabète et la glycogénèse animale, Paris, 1877.

With regard to those of congenital origin, Bruns [10] has reported that, in several cases of glioma of the pons, he has also found minute cysts lined by ependyma. These were considered as separations from the primary neural tube. Stroebe likewise found small cysts lined by columnar epithelium, in connection with gliomas of the brain. Thus, abnormalities in the primary neural tube anywhere along its course may be the focus of a morbid proliferation. The dermoid cysts may be similarly regarded as of congenital origin. These are exceedingly rare. Cushing reports but one case in his large experience. Another variety of congenital cyst, described by Heschl and Kundart, is the so-called porencephalic type, in which a defect exists in the cortex extending down to the ventricle. This occurs usually in the region supplied by the middle cerebral artery.

Cysts of parasitic origin are due either to the cysticercus or, more rarely, to the echinococcus. Hunt [6] states that they may be differentiated pathologically from the congenital group thus: 1. In the congenital type, the cyst wall throughout is made up of medullated nerve fibers and glia. 2. The cyst is not intercalated but forms an integral part of the stem. 3. There are remnants of epithelial lining present.

Traumatic cysts around penetrating spicules of bone are at times encountered and may give rise to considerable destruction of brain tissue. Hoppe [11] cites a case in which a cyst the size of a cherry developed in the substance of the left temperosphenoidal lobe as a result of a depressed fracture. The fracture was overlooked because it was covered by the temporal muscle.

Various circulatory disturbances occurring in the brain may give rise secondarily to cyst formations. The blood cysts which result from cerebral or cerebellar apoplexy and those following cerebral softening after embolism may be included in this group.

Inflammatory processes involving the brain substance may be responsible at times for the presence of cysts. It is a well known fact that the power of brain cells to regenerate is limited, and so with the removal of the débris resulting from the breaking down of the brain tissue there develops a defect which may go on to cyst formation.

Localized encysted cerebrospinal fluid has been frequently encountered on the surface of both the cerebellum and the cerebrum. Placzek and Krause describe the condition as resulting from inflammatory changes in the arachnoid, which is thickened and may be united to the dura by adhesions. Fluid collects within the meshes of the arachnoid and is walled off by these adhesions. Such changes may also occur

10. Bruns: Geschwulste des Nervensystem, 1908; Neurol. Centralb. 1893, 1896.

11. Hoppe, H. H., in Tice: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc. **9**:632.

secondary to localized meningo-encephalitic attacks with cortical destruction, seen in children, when they usually occur with infantile cerebral palsy as an underlying pathologic condition. This group constitutes the so-called arachnoidal cysts.

We come finally to a group which result from secondary degenerative changes. These occur in the various neoplasms involving the brain, and are sometimes referred to as simple serous cysts, or as cystosarcoma, cystoglioma, etc. Fraenkel reports in great detail a series of eight cases, three cerebral and five cerebellar. Of these, the three cerebral and one of the cerebellar cases were due to degenerative softening of gliomatous origin. In the group of four remaining cerebellar cysts, one was due to softening of a carcinomatous metastasis, one to hemorrhagic softening, one to anemic softening resulting from marked vascular disease and one was without any associated condition.

In exactly which group the case presented in this report belongs, according to the above classification, it is rather difficult to state. By a process of elimination, we would be inclined to list it among the growths of congenital origin. The chemical analysis of its contents establishes its proliferative nature, while the pathologic picture is obscured by secondary inflammatory changes.

MALIGNANT HYPERNEPHROMA IN CHILDREN *

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REPORT OF CASE

History.—December 5, 1921, K. T., a girl, aged 4 years and 3 months was brought to the University Hospital because of convulsions alternating with a semistuporous condition. The father and mother, native-born Americans, without apparent endocrine abnormalities, had always been in good health and had a 7 year old boy, who was free from disease. There was no history of chronic diseases in the family. The patient was normal at birth, weighing 7 pounds (3,175 gm.), and had an uneventful feeding history. Dentition began at 11 months, and had proceeded normally. At 15 months, the child was walking, and at 18 months, she was able to say several words. Until the onset of the convulsions, she was well developed mentally, being able to learn and recite little rhymes at the age of 3½ years. Increase in weight and stature had always been steady, without any noticeably sudden changes. The mother said she had always been a "fuzzy" baby, referring to the prominent lanugal hair which covered the whole body. At about 3 years, the hair on the pubes began to increase in amount, length and pigmentation, but this did not particularly impress the parents, who gave information concerning it only after questioning. She had had chicken-pox, and, at the age of 3 years, had influenza, with a complicating bronchopneumonia, from which recovery was complete in three weeks.

October 20, when 4 years and 2 months old, she was suddenly, without preceding apparent illness, attacked by a practically unilateral convulsion causing rhythmic jerking of the left side of the face, the left arm, hand and leg. It lasted three hours, and she was unconscious during this time. For the next six days, she seemed as well as usual, except for a tendency to fall when walking. November 4, a second attack affected the right side in a similar manner and, although it was of shorter duration and less severe, the child did not recover her usual mentality or physical ability, being unable to walk alone, and acting dull and stupid. Her appetite became ravenous, and she cried constantly for food. The parents noticed an increasing abdominal distention and an increase in the size of the external genitals. A third convulsion occurred, November 22, and this time affected the left side again. From then until admission to the hospital, she had been semistuporous and had not talked much except to ask for food. She had given no evidence of blindness, headache or other pain, and had not vomited. The mother said there had been no cough, fever, diarrhea or urinary abnormalities. The patient had never menstruated.

Examination.—At the time of admission, she appeared acutely ill, lying motionless on her back and not noticing her surroundings unless aroused. The rectal temperature was 99.4 F., pulse 94, respirations 24. She could not stand or sit alone. Development was fair and nutrition excellent (Fig. 1). When disturbed, she asked for food in a monotonous, coarse and rather low-pitched voice. The facial expression was stolid and the eyes were staring. The whole body was covered with prominent lanugal hair; the eyebrows and eyelashes were unusually long; the hair of the scalp was abundant and extended

* Received for publication, April 25, 1923.

* From the University of Michigan Hospital, Department of Pediatrics and Infectious Diseases, Dr. D. M. Cowie, director.

well down on the forehead; the upper lip and chin were covered with slightly pigmented hair about 0.5 cm. long; the axillae showed a moderate amount of coarse hair. There was a marked tendency toward perspiring in the palms, on the soles and in the axillae. There was no abnormal pigmentation of the skin. The breasts were normal for a girl of her age. The head appeared large, and the parietal bosses were prominent. The eyes were staring, and

Fig. 1 (Author's Case).—The good nutritional state is evident.

vision was apparently present. The pupils were round and equal, and reacted to light. There was a varying and indefinite limitation of extraocular motion to the left. The fundus showed no choking of the disks; a point confirmed by Dr. W. R. Parker. The ears, nose and mouth were normal; the tonsils were not enlarged. The neck was short and stocky; the thyroid gland could not be felt.

Percussion and auscultation of the chest revealed no pathologic condition of the lungs or heart. The left border of the heart was 7.5 cm. from the mid-

sternal line. The abdomen was above the level of the rib margin and was tympanitic, this distention rendering palpation difficult and unsatisfactory. With the aid of deep percussion, an indefinite tumor mass was made out in the right flank just under the liver margin, the latter being 2.5 cm. below the costal margin. Examination of the genitals revealed prominent mons verneris and large labia majora, sparsely covered with pigmented hair averaging 3 cm. in length (Fig. 2). The labia minora were of adult type, and the clitoris was of adult size, measuring 2.2 cm. in length, and having a redundant prepuce. The meatus urinarius and vaginal orifice were in the normal relation. The internal genital organs could not be palpated by rectal examination. The hands were short and broad, with stubby fingers. The left arm was rather

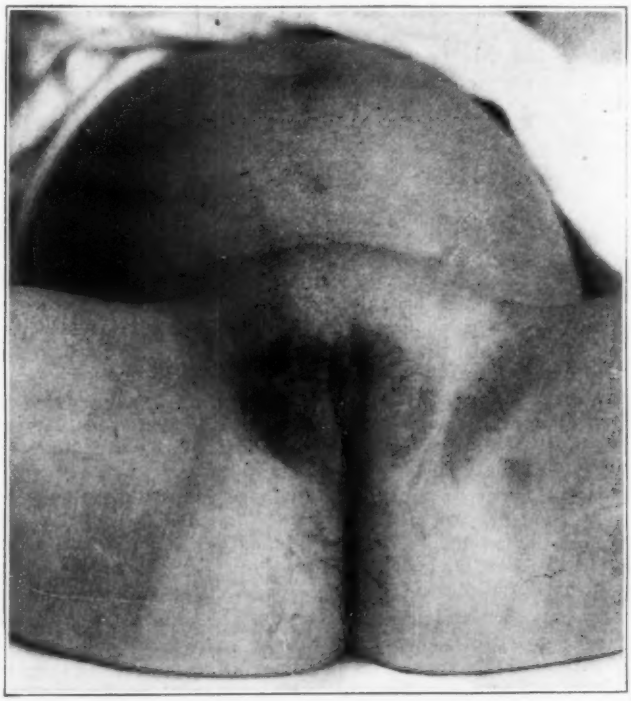

Fig. 2 (Author's Case).—Appearance of genital region, showing prominent mons veneris, adult type of vulva and distribution of hair.

rigidly held, and showed little voluntary motion, but not true spasticity, and no paralysis could be made out. The lower extremities were not spastic and showed no atrophy or paralysis. Lack of satisfactory cooperation precluded accurate study of extra-ocular, facial and lingual movements. The biceps, patellar and Achilles reflexes were present, equal and not exaggerated. There was no ankle clonus, and plantar irritation caused plantar flexion of all the toes. Associated movements could not be studied, but there was no tremor or evident asynergia in the voluntary movements. Pin pricks were evidently felt on all skin surfaces, causing complaint and motion. There was no sign of meningeal irritation.

Clinical diagnosis: The probability of an abdominal tumor in a girl of 4 years, showing heterosexual precocity, suggested the clinical diagnosis of malignant hypernephroma.

Laboratory findings: The urine was normal, except for a few leukocytes in the sediment. Examination of the blood revealed: hemoglobin, 88 per cent. (Sahli's test); leukocytes, from 12,000 to 17,000; erythrocytes, from 5,460,000 to 4,880,000; differential count: total mononuclears, 40 per cent., with normal distribution; total polymorphonuclears, 60 per cent., with normal distribution; smear: erythrocytes, normal in size, shape and staining reactions. Blood pressure was: systolic 145-160; diastolic 90-100. The spinal fluid was clear, the pressure moderate; the cells numbered two per cubic millimeter; there was no albumin nor globulin; the Wassermann reaction was negative; Lange colloidal gold and mastic curves were negative; Pirquet skin tuberculin test was negative. Tests of sugar tolerance revealed no glucose in the urine following ingestion, on an empty stomach, of 40 gm. of glucose (2.5 gm. per kilogram of body weight). The blood sugar curve, before ingestion of 1.75 gm. of glucose per kilogram of body weight, dissolved in 120 c.c. of water, taken after fasting fourteen hours, was 0.105 per cent.; at thirty minutes, 0.152; forty-five minutes, 0.150; one hour and twenty minutes, 0.143; two hours and fifteen minutes, 0.141; three hours and ten minutes, 0.100.

Measurements: The standing height (supported) was 96.0 cm.; sitting height, 55.0 cm.; weight, 34.5 pounds (15.7 kg.); pelidisi (Pirquet), 99 per cent.; circumference of head, 50.7 cm.; of chest (at nipple), 52.0.; of abdomen (greatest), 54.2 cm.; crown to umbilicus, 44.0 cm.; umbilicus to sole of foot, 56.5 cm.

Diagnosis: The presumptive evidence of an abdominal tumor in a girl, aged 4 years and three months, showing heterosexual precocity, as evidenced by hypertrophied clitoris, deep voice, and hypertrichosis of distribution characteristic of the male, and brought to the hospital because of convulsions alternating with lethargy, suggested the diagnosis of hypernephroma, with a possibility of intracranial metastasis. To confirm our clinical diagnosis, it was necessary to prove the presence of the suspected tumor mass in the right side of the abdomen. The patient's peritoneal cavity was inflated with carbon dioxid gas introduced through the abdominal wall with an 18-gage needle, and measured by an apparatus similar to that described by Peterson[1] and others. Roentgenograms were taken with the patient on her back, right side and left side, before the carbon dioxid had been appreciably absorbed (inside ten minutes). The right oblique view (patient on left side) showed a mass which at that time was interpreted as being a kidney tumor. Repetition of the procedure five days later yielded a better film, in which it was possible, as reported by Dr. Van Zwaluwenburg, to see above and lateral to the right kidney shadow "another and less clearly defined shadow which appears to be distinct, cleancut in outline, about one-half the size of the kidney. The kidney is evidently displaced downward." The liver shadow was clearly seen overhanging the kidney and tumor shadows. This unusual opacity was interpreted without hesitation as representing a tumor in the region of the right suprarenal.

Two roentgenograms of the skull showed a normal sella turcica, and no evidence of any erosion of cranial bones. The lung roentgen-ray examination gave no evidence of intrathoracic metastasis. Three weeks after admission, the spine failed to show any sign of metastasis by roentgenogram.

Course.—Since the patient had no true localizing neurologic signs in spite of the convulsions, and no evidence of lung metastases, the advisability of attempting to remove the primary tumor was considered. She was seen by Dr. M. M. Peet, who, after the parents urged surgical intervention, consented to perform an exploratory laparotomy. This was delayed for some time by the occurrence of four attacks of convulsions at intervals of several days, each series leaving the patient in such poor general condition that interference was considered inadvisable. The convulsions involved the right and left sides alternately and were not followed by any neurologic localizing signs or any

1. Peterson, Reuben: Surg., Gynec. & Obst. **33**:154 (Aug.) 1921.

choking of the optic disks. During this delay, the abdominal distention decreased and the tumor mass became progressively more palpable.

Operation.—Jan. 11, 1922, a large tumor was found behind the peritoneum, covering the upper pole of the downwardly displaced right kidney, and extending upward to the junction of the hepatic veins with the inferior vena cava. It was encapsulated, somewhat lobulated and very friable, most of the center being necrotic and containing extravasated, changed blood. Complete removal was impossible because of the extent of the mass and the patient's poor condition. In spite of blood transfusion she died, four hours after the operation.

Microscopic Examination.—This confirmed the clinical diagnosis of malignant hypernephroma of the right suprarenal cortex.

Necropsy Data (Drs. Warthin and Weller).—The panniculus was 3 cm. thick over the pubes. Section of the breasts showed no glandular tissue. The thymus was very small, showing fibroid atrophy; the corpuscles of Hassal were quite numerous. The heart showed no pathologic changes except a slight right-sided dilatation. The pleura was not adherent. The lungs were studded with numerous nodules, those beneath the pleura varying from 0.5 to 1.5 cm. in diameter. These were sharply circumscribed, soft, yellowish, neoplastic masses, which on section resembled medullary carcinoma, although the general architecture was slightly suggestive of suprarenal cortex (malignant hypernephroma). The lungs were edematous and congested. The thyroid was small, the colloid abundant. The gastro-intestinal viscera and adnexa were normal except for slight hyperplasia of the lymph nodes and Peyer's patches. The left suprarenal was thinner than normal, and on section appeared hypoplastic. The situation of the right suprarenal was occupied by a large neoplastic mass, measuring 10 cm. in greatest length, 6 cm. in width and 5 cm. in thickness, notwithstanding the fact that part of it had been removed surgically. This mass was retroperitoneal but had elevated the peritoneum sufficiently to cause its attachment to the under surface of the liver. The kidney had been pushed downward and was uninvolved in the new growth. On macroscopic section, normal suprarenal tissue was not found. The mass was friable and necrotic in most places, but the firmer portions were light yellow, with a fatty appearance. Microscopically, some areas resembled a suprarenal cortex. The atypical portions more closely resembled a medullary carcinoma, but many of the cells contained lipoids. Some areas showed a marked perivascular arrangement of the cells, more like an angiosarcoma. The kidneys showed cloudy swelling and acute congestion. The vaginal orifice admitted the finger with slight difficulty; the vaginal canal measured 6 cm. in length. The uterus was undeveloped, measuring 3 cm. from fundus to external cervical os. The ovaries were free, 2.0 by 0.5 cm., and showed on section an unusual number of large cystic follicles, but no evidence of menstruation.

Examination of Brain (Dr. A. M. Barrett of the Department of Psychiatry).—The brain had been hardened in 10 per cent. formaldehyd for nine days. It had a length of 16.2 cm. and a breadth of 12.8 cm. In volume, it gave the impression of being larger than usual for a child of this age. The pia mater was clear, with slight congestion of the larger veins. The convolutions of the convexity were normally formed but had not reached full development. In a few places, there were small areas in which the surface of the convolutions appeared softened.

The base of the brain showed erosions of the tip of the temporal lobe from mechanical injuries during its removal. The basilar artery was partly filled with blood clot. At a point about 1 cm. from its bifurcation, there was a small patch of thickening of the artery wall.

Vertical sections of the brain showed no gross abnormalities aside from the small areas of superficial softening. In these, the cortex appeared macerated and separated easily from the underlying white substance.

The pineal gland was somewhat flattened, and measured 7 mm. in width and 5 mm. anteroposteriorly.

Histologic examination revealed a number of pathologic alterations. The pia mater of the convexity was not thickened, and there was no infiltration. In a number of places, notably near the areas of softening, a number of arteries showed marked arteriosclerotic changes. These varied from slight thickening of the intimal layer to an extreme narrowing of the lumen, with an hypertrophy of the intima. The elastic coat was not abnormal. In one vessel, presenting slight thickening of the intima, there were fragments of this layer separated from the underlying coats and extending into a tangled mass of fibers filling the lumen of the vessel.

Sections through the areas of softening showed small patches in which the parenchyma had disappeared, leaving a defect filled with strands and islands of swollen vessels with scattered epithelial cells. Bordering this was an area in which the continuity of the tissue had not been broken but showed dense infiltration with epithelioid cells, marked reduction of the number of nerve cells and a great number of large progressive forms of neuroglia cells. The blood vessels in this area showed swelling of their walls and early proliferative changes. For some distance away from this more markedly altered area, the region showed loss of nerve cells, marked glia hypertrophy, and slighter changes in the blood vessels. These changes involved only the nerve cell layers of the cortex. In their type, they were characteristic of the reaction that occurs from occlusions and arteriosclerosis of the vessels of the pia mater.

The pituitary gland showed normal relations between the glandular and nervous portions, the stalk, and the connective tissue of the capsule in this region. There was a dense accumulation of cells. These lay in clumps and infiltrated the connective tissue for some distance. They were chiefly large mononuclear forms with a large amount of cytoplasm. In most of these, the cytoplasm was compact and homogenous; in others, highly vacuolated. There were also, in places, a considerable number of lymphocyte-like nuclei lying in patches along the stalk.

Diagnosis: Arteriosclerosis of the pial vessels; multiple superficial cortical softenings and pathologic cellular accumulations in the region of the stalk of the pituitary gland were diagnosed.

THE LITERATURE

Precocious sexual development has always attracted much attention, especially when occurring in very young children. The literature contains numerous references to such cases, many of them without evident pathologic basis. The manifestations of precocity are variable. Both the secondary and primary sex characteristics may be involved, resulting in true pubertas praecox, with spermatogenesis and its accompanying manifestations in the male, and with ovulation and menstruation in the female. The term should be carefully restricted to those cases showing the physiologic processes necessary for propogation, and not loosely applied to some of the secondary changes to be noted later. These secondary sex characteristics may be the only ones prematurely developed, and may be either homosexual, the accentuated characteristics being the ones normally found in the sex affected, or heterosexual, showing certain changes considered typical of the opposite sex. Krabbe[2] has recently applied the term virilism to the following syndrome of male characteristics appearing in the female, regardless of the age: hypertrichosis, including face, hyper-

2. Krabbe, K. H.: New York M. J. **114**:4 (July 6) 1921.

trophy of the clitoris and deepening of the voice. This syndrome fits the majority of reported cases of suprarenal cortex tumors, and is heterosexual precocity but not true pubertas praecox. It is sometimes accompanied by premature body growth either in the form of (*a*) fat deposits, (*b*) hypertrophied musculature (herculean type) or (*c*) skeletal overgrowth resulting in gigantism.[3] Pelizzi has suggested for this combination the term macrogenitosomia praecox.

The etiology of the numerous cases of abnormal sex and body development in children has been definitely determined in only a small proportion of recorded cases. For a general survey of this interesting field two recent articles, Leiner[4] and Tierney[5] furnish a large bibliography. According to Guthrie and Emery,[6] atavistic tendency to early maturity, or hastened old age (progeria) may account for some of the cases in which there are no pathologic findings. Although the thyroid gland is intimately related to body and sex growth, as evidenced by changes in it associated with puberty, menstruation and pregnancy, and changes in the body and genitals associated with congenital or acquired hypothyroidism or athyroidism, it is true that precocious puberty does not occur with tumors of this gland. Linser[3] quotes Fritsche and Klebs as implicating the thymus in growth disturbances. Frohlich's syndrome furnishes a good example of the influence of the pituitary on the somatic and genital systems, and acromegaly is an expression of its effect on somatic growth; but here again true early puberty is not intimately associated with tumors, although retardation of sex development may accompany decreased function of the gland. Occasionally, tumors of the pineal body produce sexual and other forms of physical precocity. Of the seventy or more reported pineal tumors, about twenty-four have been in children (McCord[7]), and only about four were in females.[8] In 1912, Glynn[9] was able to find only five cases proved by necropsy, and associated with sexual precocity. These were all in boys. It is thus readily seen that much confusion exists concerning the actual number of cases of pineal tumors in children causing sex and somatic changes, and the proportion of males and females, although it is clear that the condition predominates in males.

Pathologic changes in the gonads (testis and ovary) are probably the commonest cause of true precocious puberty in the cases showing

3. Linser, P.: Beitr. z. klin. Chir. **37**:282, 1903.
4. Leiner, J. H.: Endocrinology **4**:369 (July-Sept.) 1920.
5. Tierney, J. L.: Med. Clinics N. America **6**:31 (July) 1922.
6. Guthrie, L., and Emery, W. d'E.: Tr. Clin. Soc. London **40**:175, 1907.
7. McCord, C. P.: Tr. Am. Gynec. Soc., 1917; Surg., Gynec. & Obst. **25**:250 (Sept.) 1917; The Pineal Gland in Relation to Somatic, Sexual and Mental Development, J. A. M. A. **63**:232 (July 18) 1914; Interstate M. J. **22**:354, 1915.
8. Baar, H.: Ztschr. f. Kinderh. **27**:141, 1920.
9. Glynn, E. E.: Quart. J. Med. **5**:157, 1911-1912.

lesions at necropsy. Tumors of these organs usually cause homosexual prematurity, and surgical removal has been known to result in amelioration of the condition or even complete restoration to normal. The relation of the suprarenal cortex to somatic prematurity was first emphasized by Linser,[3] who collected a few cases showing gigantism, as he called it, associated with tumors of the suprarenals. In 1905, Bulloch and Sequeira [10] collected, and presented in a masterly way, the previously accumulated evidence pointing to the effect exerted on the genital system by the suprarenal glands. They discussed twelve cases of malignant conditions of the suprarenal cortex in children, citing in addition five necropsies which showed hypergenitalism to be associated with simple hypertrophy of the suprarenal cortex, and another series of cases of underdeveloped genitals in which the cortex was hypoplastic or aplastic. It is also interesting to note that they mentioned thirteen cases of primary suprarenal tumors in young children unassociated with any precocious sexual development. Carter [11] has recently emphasized the fact that tumors of the suprarenal medulla do not cause sexual prematurity, but usually evidence themselves first by metastases and the resulting local symptoms. Hypernephroma of adults with lack of sex changes can be explained by the relative stability of the generative system during adult life. In 1911, Glynn [9] collected five more cases of suprarenal cortex tumors, and these, together with the four reported since that time, make a total of twenty-one cases of this condition in children, as verified by operation or necropsy. A brief summary of these cases will help us to formulate a more inclusive clinical picture.

William Cooke[12] (1756): A girl, aged 7 years, enormously fat with a large skeleton, and having copious hair on the face and genitals, died in convulsions. Necropsy revealed internal hydrocephalus and a large tumor extending from the upper pole of one kidney to the upper pole of the other. Neither suprarenal was found. There was no microscopic report.

Bevern and Romhild[13] (1802): A girl, aged 3½ years, fat, and "looking like a woman of 20," had abundant hair on the face and pubes. Necropsy revealed a large tumor in the left abdominal cavity. The exact attachments were not mentioned, nor were the suprarenals mentioned. The case was apparently typical clinically, but pathologic proof was insufficient.

Tilesius[14] (1803): A girl, aged 4 years, with very adipose body and large (fat?) mammae, had well developed pubic hair. Necropsy revealed a tumor the size of a goose egg in the left suprarenal, and metastases to the liver.

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10. Bulloch, W., and Sequeira, J. H.: Tr. Path. Soc. London **56**:189, 1905.
11. Carter, W. E.: Medullary Malignancies of Suprarenal Gland with Report of Cases, Am. J. Dis. Child., **22**:244 (Sept.) 1921.
12. Cooke, William: Phil. Tr. Roy. Soc. London, 1756. This could not be verified; quoted from Linser (Footnote 3), and Bulloch and Sequeira (Footnote 10), who could not verify it.
13. Bevern and Romhild: J. d. prakt. Arznk. u. Wundarznk. **14**, Part 3, p. 141.
14. Tilesius: Quoted by Linser (Footnote 3).

Pitman[15] (1865) and Ogle[16] (1865): A girl, aged 3 years, normal at birth, had presented symptoms for eight months. At 3 years, she was stout, 34½ inches (86 cm.) tall, and weighed 44 pounds (20 kg.). She had a sullen expression, a rude and savage disposition, a rough voice and a voracious appetite. The skin was "gipsy color." There was a general hypertrichosis, with heavy eyebrows, moustache and prominent pubic hair. The genitals were "precociously developed." A tumor was palpable in the left side of the abdomen. Necropsy revealed a tumor of the left suprarenal, weighing 2⅛ pounds (nearly 1 kg.), with metastases to the liver and lungs. The other organs including the uterus and ovaries were normal. The tumor was a "large mass of encephaloid cancerous growth."

Colcott-Fox[17] (1885): A girl, aged 2 years, normal at birth, but "enormous" at 10 months, had a ravenous appetite, dull intellect and dusky pallor of the skin. The vulva, labia and clitoris were precociously developed and the pubic and body hair was prominent. There was a tumor in the left side of the abdomen. At necropsy, this growth was found to replace the left suprarenal. Its weight was 1½ pounds (about 0.7 kg.). The uterus and ovaries were large. There were metastases to the lungs. The tumor was a giant-cell sarcoma.

Dickinson:[18] A girl, aged 3 years, of dull intellect, and having "gypsy" colored skin, a harsh voice and ravenous appetite, had had hair on the pubes since 1 year of age. The condition of the genitals was not recorded. Necropsy revealed a tumor of the suprarenal (side not given), with metastasis to the liver. The growth was "encephaloid."

Orth[19] (1893): A girl, aged 4½ years, normal at birth, had had symptoms since the age of 1 year. The clitoris became like a small penis, and the other external genital organs were precociously developed. There was hair on the pubes, and the face was bearded, requiring shaving for the last six months. A tumor had been palpable in the right side of the abdomen for two and one half years. At necropsy, the growth was found to replace the right suprarenal. There were metastases to the liver and lungs. The tumor was a carcinoma (hypernephroma?).

Dobbertin[20] (1900): A girl, aged 14 months, born with a tumor in the abdomen, had hair on the labia majora, body, cheeks and chest. The genitals were not mentioned. Somatic development was normal. At operation, the tumor, which replaced the left suprarenal, and left kidney were removed. At necropsy, metastases behind the manubrium sterni were revealed. The tumor was a "congenital carcinoma."

Miller[21] (1903): A girl, aged 2 years, normal at birth, had presented symptoms since 1½ years: abdominal swelling and hypertrophy of the labia majora and minora, with sparse hair on the former. The clitoris was enormously enlarged, 1 inch (2.5 cm.) long, with definitely retractable prepuce. Operation revealed a vascular tumor of the right suprarenal. Removal was not attempted. The patient survived exploration, and passed through an attack of measles and bronchopneumonia, dying eleven months later. The history of the intervening period and necropsy findings were reported by White and Nisbet.[22] The child resembled a "little old woman," with thick neck, prominent eyes and dark skin. Necropsy revealed a large tumor of the right suprarenal. The clitoris was 4 cm. long, with a definite prepuce. The pubic hair was abundant. There

15. Pitman: Lancet **1**:175, 1865.
16. Ogle, J. W.: Tr. Path. Soc. London **16**:250, 1865; Med. Times & Gaz. **1**:532, 1865.
17. Colcott-Fox, T.: Tr. Path. Soc. London **36**:460, 1885.
18. Dickinson, W. H.: Quoted by Colcott-Fox (Footnote 17).
19. Orth, Johannes: Arb. a. d. path. Institut. in Göttingen, Berlin, Virchow, 1893, p. 75.
20. Dobbertin: Beitr. z. path. Anat. u. z. allg. Path. **28**:42, 1900.
21. Miller, D. J. M.: Arch. Pediat. **20**:932, 1903.
22. White, C. J., and Nisbet, V.: Arch. Pediat. **21**:943, 1904.

were metastases to the liver, mesenteric nodes and the right lung. The tumor was a hypernephroma.

Linser[9] (1903): A boy, aged 5 years and 7 months, normal at birth, but presenting symptoms for the last 15 months, resembled a youth of from 16 to 18 years. He was 138 cm. tall, weighed 39 kg., and had twenty-eight teeth. All eight carpal ossification centers were present. There had been hair on the mons veneris for one year. The penis was from 8 to 9 cm. long (from 12 to 14 cm. in erection); the testes were the size of pigeon's eggs. A large tumor was palpable in the left kidney region. At operation, no attempt was made to remove the mass. Necropsy revealed a large left suprarenal tumor, with rupture into the vena cava, and metastases to the lungs. The testes showed no spermatogenesis. The thyroid, hypophysis and pineal glands were normal. The thymus was not found. The tumor was a hypernephroma.

Bulloch and Sequeira[10] (1905): A girl, aged 11 years, normal at birth, was intellectually dull; of brunette complexion; had a large face, and "looked like a stout little woman of about 40 years." The height was 4½ feet (135 cm.), the weight, 87 pounds (39.5 kg.). There was hair on the chin, lips and pubes and in the axillae. The breasts were large, resembling those of a sexually mature woman. The patient had menstruated during the last fifteen months (since the age of 10 years). There was a tumor in the left side of the abdomen, which necropsy revealed replacing the left suprarenal. The growth weighed 3 pounds and 1 ounce (1.6 kg.). The thyroid and parathyroid were hypertrophied. The uterus showed enlargement of the cervix. The ovaries were fairly large. The corpora lutea were found. There were metastases to the liver and lungs. The tumor was a carcinomatous hypernephroma.

Ritchie[23] (1905): A girl, aged 4 years, who had abundant pubic hair, had been considered an hermaphrodite, but Prof. Arthur Thompson said that the genitals were normal except for size. In this respect, they resembled those of a developing woman. Menstruation had not occurred. Death followed an osteotomy. Necropsy revealed an unsuspected tumor of the suprarenal (side not given). The growth was "sarcomatous."

Adams[24] (1905): A boy, aged 14 years and 4 months, normal at birth, but presenting symptoms since the age of 10 years, was a "sturdy little man," of great muscular strength. He had had a beard for the last two years; "puberty set in at the age of 10." A tumor was palpable on the left side of the abdomen. Exploratory laparotomy revealed an inoperable tumor in the region of the left kidney. The patient died seventeen months later. Partial necropsy revealed a tumor, weighing 8½ pounds (3.8 kg.), replacing the left suprarenal, encapsulated, and the kidney uninvolved. The liver was enormously enlarged, weighing 15½ pounds (7 kg.), and infiltrated with yellowish tumor masses. The spleen showed metastases. The right suprarenal was normal. The tumor was a malignant hypernephroma (perithelioma).

Walker (verbatim report by Richards,[25] 1905): A girl, aged 8½ years, whose symptoms began at 5 years, became very stout, and developed excess hair on the pubes, face and chin, with silky beard and whiskers. The external genitals were not unduly developed. A tumor was palpable in the left hypochondrium. The abdomen was tapped for ascites. Partial necropsy revealed: left kidney size of coconut, consisting entirely of new growth; right kidney about one-half this size, destroyed by growth; metastases to liver. The suprarenals were not definitely mentioned. The tumors were not sectioned. The case was clinically typical, but the condition was not definitely proved pathologically.

Guthrie and Emery[26] (1907): A boy, aged 4 years and 9 months, normal at birth, had presented symptoms for two years. He gradually

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23. Ritchie: Quoted by Bulloch and Sequiera (Footnote 10).
24. Adams, C. E.: Tr. Path. Soc. London **56**:208, 1905.
25. Richards, Owen: Guy's Hosp. Rep. **59**:217, 1905.
26. Guthrie, Leonard, and Emery, W. d'E.: Tr. Clin. Soc. London **40**:175, 1907.

became very stout, like a "burly brewer's drayman." The height was 36 inches (90 cm.); weight, 43½ pounds (about 20 kg.). There was flabby fat on the shoulders, trunk, arms, abdomen and breasts. The eyebrows were bushy, and there was coarse hair on the pubes. The genitals were "not unduly developed." Convulsions occurred three months previous to admission to hospital. The patient died of acute tuberculosis. No abdominal tumor was palpable. At necropsy, in addition to disseminated miliary tubercles, a tumor the size of a large walnut, replacing the left suprarenal, was revealed. The right suprarenal was not found. The thymus, thyroid, hypophysis, epiphysis and testes were normal. The latter did not show spermatogenesis. There were no metastases. The tumor was a malignant hypernephroma, carcinomatous and very complex.

Dunn and Glynn[9] (1912): A girl, aged 5 years, whose symptoms began at 3 years, had precocious body development, was "unusually tall," fat and flabby. The hair was profuse on the scalp, upper lip, pubes and back. There was no hypertrophy of the clitoris or mammae. Menstruation had not occurred. Six weeks before death, a tumor was palpable in the right side of the abdomen. Convulsions occurred during the latter part of the illness. Necropsy revealed a tumor, weighing 2¾ pounds (1.25 kg.), 7½ by 5 by 4 inches (3 by 2 by 1.6 cm.), replacing the right suprarenal. It was encapsulated, free from the kidney, and showed a structural arrangement similar to that of the cortex. The areas of Langerhans were prominent. There was exhaustion of colloid in the thyroid. The pituitary and left suprarenal were normal. There were no metastases. The tumor was a malignant suprarenal hypernephroma.

French[27] (1912): A girl, aged 7 years, developed pubic hair at 18 months, and the external genitals became hypertrophied. A large tumor was palpable in the left upper section of the abdomen. A diagnosis of suprarenal tumor was made. At operation, the tumor and the left kidney were removed. Necropsy revealed metastases to the lungs. The tumor was a perithelioma (hypernephroma).

Jump, Beates and Babcock[28] (1914): A girl, aged 7 years, one of twins, normal at birth, at 1 year began to show phenomenal body development and physical strength. At 7 years, she was 53 inches (132.5 cm.) tall, weighed 90 pounds (41 kg.), and had a deep voice, the larynx being like that of a man. The child was well developed mentally. There was hair on the pubes, legs, trunk and chin (distinct beard), and in the axillae. The skin perspired freely. The labia were large. The clitoris was 2.5 cm. long, and grooved on the under surface. The breasts were relatively undeveloped. Menstruation had not occurred. A tumor was palpable in the right side of the abdomen. A diagnosis of tumor of the right suprarenal cortex was made. Removal was attempted, but was unsuccessful, death ensuing in three hours. Partial necropsy revealed that the growth involved the right kidney, without demarcation. The left suprarenal was normal. The uterus and ovaries were infantile. There was no evidence of metastasis in the abdomen. The tumor was a hypernephroma.

Van den Bergh[29] (1915): A girl, aged 3 years, showed "premature development of secondary sexual characteristics" and of the external genitals, without menstruation. At operation, a tumor was removed from the region of the left suprarenal. The growth, which weighed 2 kg., was a carcinomatous hypernephroma.

Schiff[30] (1918): A girl, aged 2 years, had presented symptoms for two and one half months: a ravenous appetite, heavy voice and adiposity. The weight was 11.6 kg., height, 74 cm. The pubic hair was 3 cm. long, and there was a

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27. French, Herbert: Cited by Glynn (Footnote 9); Index of Differential Diagnosis, Ed. 2, New York, William Wood & Co., 1917, p. 164.

28. Jump, H. D.; Beates, H., Jr., and Babcock, W. W.: Am. J. M. Sc. **147**:568, 1914.

29. Van den Bergh: Nederlandsch. Tijdschr. v. Geneesk., 1915, p. 2217.

30. Schiff, E.: Jahrb. f. Kinderh. **87**:519, 1918.

moderate beard. The breasts were normal, and no unusual development of the genitals was noted. There was a palpable tumor in the right side of the abdomen. A diagnosis of hypernephroma was made. An exploratory operation was followed by death. Necropsy revealed a tumor, 16 by 11 by 6 cm., replacing the right suprarenal, separate from the kidney. The thymus, left suprarenal, uterus and ovaries were normally developed. The hypophysis and epiphysis were slightly enlarged, the former showing an increase of eosinophils. The acini of the thyroid were small; the colloid was scanty. Metastasis was not noted. The growth was a hypernephroma.

Ambrozic and Baar[31] (1920): A girl, aged 3 years, whose symptoms began at 1 year, had a mannish voice, looked like a child of 6 years, and was intellectually advanced. The height was 105 cm., weight 18.3 kg. The musculature was well developed, and there were eight centers of ossification in the wrist. The labia were large and lipomatous; the clitoris was like a little finger, and grooved on the under surface; the breasts were undeveloped. The hair was heavy on the pubes, labia majora and around the arms ,and scanty in the axillae. A tumor was palpable in the left side of the abdomen. A diagnosis of malignant suprarenal tumor was made. At operation, the left kidney and the tumor were removed. Death ensued the same night. At necropsy, the internal generative organs were normal, except for a proportionately large cervix uteri and vagina. There was a cyst in the region of the pineal gland, but the latter was free. Other organs of internal secretion were normal. There were metastases to the lungs and the right temporo-occipital lobe of the brain. The tumor, which was encapsulated, septate and gray-red, was a malignant epithelial growth, with a structure resembling in places that of the zona fasciculata (hypernephroma).

COMMENT

Of the twenty-two cases of malignant hypernephroma verified by operation or necropsy, nineteen occurred in females and only three in males. In some of the reports, the data are incomplete and make accurate comparative study unreliable. A tumor was clinically demonstrable in the majority of cases, and there seemed to be no preference for either side. With apparently but one exception, the patients were normal at birth, but most of them presented symptoms within the first four or five years of life. The effect on somatic development was not uniform; two males showing marked prematurity in body strength, accompanied by precocious homosexual genital development, the other boy showing large fat deposits, flabby musculature and no undue enlargement of genitals. The females showed a much smaller percentage of somatic changes. Only one had menstruated, and she was 10 years old at the time. The great majority of the girls showed heterosexual precocity: hair on face, deep voice, overdevelopment of the clitoris and lack of development of breasts. The boys invariably showed accentuation of male characteristics. A few showed distinct pigmentation of the skin. Several had ravenous appetites. In spite of the fact that intracranial metastasis was demonstrated at only one necropsy, four patients are mentioned as having had severe convulsions. In nine cases, exploratory laparotomies were performed. The viscera showing metastases most fre-

31. Ambrozic and Baar: Ztschr. f. Kinderh. **27**:135, 1920.

quently were the lungs and liver, no author mentioning bone metastases. The other glands of internal secretion did not show any striking or constant changes. The confusing variety of pathologic nomenclature applied to the neoplasms was undoubtedly due to the fact that the microscopic appearance of these masses varied not only in different cases but also in separate portions of the same tumor. The term malignant hypernephroma seems to be most commonly used now, rather than one based primarily on morphology.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the etiology of precocious sexual development involves a consideration of the gonad (testis or ovary), pineal and suprarenal glands especially. Homosexual precocity in the male can be caused by tumors in any of the three, the order of frequency being as named above. Homosexual precocity in the female implicates the ovary in the majority of cases. Heterosexual precocity in a female child is most suggestive of a malignant condition of the suprarenal cortex or hyperplasia.

Pineal tumors have been predominant in males, but the number verified by necropsy is small. According to Marburg, these cases show three groups of symptoms: (1) sexual and somatic abnormalities from the specific effect of the pineal tumor; (2) choked disks, headache, drowsiness and vomiting, from increased intracranial pressure, and (3) focal neurologic signs, as cerebellar ataxia, nystagmus, general paralysis of the cranial nerves (especially the eye innervation group), from local pressure or extension. The neurologic changes are usually coincident with the genital abnormalities, thus helping to differentiate gonad or suprarenal tumors, which may give rise to intracranial metastasis late in their course. Even after an abdominal tumor is demonstrable, it becomes necessary to distinguish between ovarian and suprarenal tumors, which is usually possible clinically. When an abdominal tumor is merely suspected, it is hoped that roentgengrams following inflation of the peritoneal cavity with carbon dioxid will greatly assist in an early and accurate localization.

KRABBE'S HYPOTHESIS

It is well known that, in elasmobranchs, the suprarenal cortex and medulla are separate and have different anatomic structures. In higher vertebrates, including man, this separation is still indicated by the embryologic derivation of the two portions of the united gland, the cortex coming from the genital ridge in close association with the gonad; whereas, the medulla is developed from tissue closely associated with the sympathetic nervous system. This belief in a relation between the gonads and the suprarenal cortex is accentuated by the facts that suprarenals of rabbits are hypertrophied during the breeding season (Stilling); frogs show seasonal variation in the size of their

suprarenals, and castration in animals often causes enlargement of the adrenal cortex. Kohn [32] suggests that the origin of the ovary is hermaphroditic, the cortex being the differentiated female portion, but the medulla having sex-cords and interstitial cells resembling in many ways those in the testis, and coming directly from the original undifferentiated genital ridge close to the suprarenal cortex. Normally, these essentially male elements of the ovary remain rudimentary, but Krabbe [2] suggests that occasionally these cells may become incorporated in the neighboring suprarenal cortex and run wild, giving rise to neoplasms, the cells of which are not derived from the suprarenal but from essentially male genital ridge tissue, and therefore give rise to an internal secretion which causes development of male sexual characteristics.

These details are presented in the hope that early recognition of the importance of these subtle early sex changes, together with the rapid improvements being made in the demonstration of abdominal tumors, may make it possible to diagnose such cases early enough to allow successful surgical intervention. This possibility is rendered all the more probable when we remember that metastases from suprarenal cortex tumors are usually late, and that the opposite gland is almost uniformly normal according to our present anatomic and histologic standards.

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32. Kohn, A.: Arch. f. Entweklngsmechn. d. Organ., 1920, p. 47.

STUDIES OF TETANY

I. THE EFFECT OF CALCIUM CHLORID INGESTION ON THE ACID-BASE METABOLISM OF INFANTS *

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It has for sometime been a matter of observation in this clinic, and no doubt elsewhere, that infants receiving calcium chlorid for relief of the symptoms of tetany will occasionally develop hyperpnea. In these instances a marked lowering of the plasma bicarbonate may be demonstrated.

It is possible to explain an acid effect from the ingestion of calcium chlorid by assuming a more complete absorption of the chlorid ion (Cl^-) than of the calcium ion (Ca^{++}) from the gastro-intestinal tract. The probability that a large part of the calcium will form insoluble phosphates and soaps, and, in consequence, escape absorption affords ground for this surmise. If this is the case the uncovered chlorid ion must be provided before absorption with other base derived from the carbonates and dibasic phosphates of the food. The effect on acid-base metabolism of an excess of the chlorid ion over the calcium ion absorbed should be the same as would be produced by placing in the food an equivalent amount of hydrochloric acid, except to such extent as the calcium ion released from the chlorid ion interferes with the absorption of other inorganic acids and thereby offsets the increased absorption of the chlorid ion. The only other accessible inorganic acid in the food is phosphoric. A lowering of absorption of this acid by the calcium ion from ingested calcium chlorid will doubtless, to some extent, occur, owing to an increased formation of insoluble phosphates. Since, however, much of the calcium from ingested calcium chlorid may reasonably be assumed to be carried into the stools by organic acid products of digestion, a large part of an excess of the chlorid ion over the calcium ion absorbed would not be compensated for; interference with the absorption of these organic acids being of no moment from the point of view of acid-base equilibriums within the body.

The efficacy of calcium chlorid administration in relieving the symptoms of tetany being well established, definite information regarding

* Received for publication, March 21, 1923.
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the manner and extent of its acid effect is desirable. The experiments to be described in this paper were undertaken with the purpose of obtaining data on this point.

PLAN OF STUDY

The plan of study consisted in obtaining certain data from analyses of stools, urine and blood serum during a fore period, and then repeating the measurements during a period in which calcium chlorid was administered. The same diet, a usual one, was continued throughout. The data obtained from the fore period were used as a basis by means of which alterations in acid-base values during the calcium chlorid period could be noted and approximately measured. Two infants were studied in this way; Infant W., 5 months old, weighing 5.9 kilograms, regarded for the purposes of this study as a normal infant, and Infant H., 4 months old, weighing 4.3 kilograms and presenting, before calcium chlorid was given, marked symptoms of tetany. Infant W. was given each day 1,000 c.c. of 10:20 milk, with 5 per cent. added cane sugar. Infant H. received each day 700 c.c. of a 12:20 mixture, with 5 per cent. of added cane sugar. During the calcium chlorid periods, 2 gm. of calcium chlorid each day were added to the milk of the normal infant, and the infant with tetany was given 1.5 gm. each day.[1] The urine and stool collection periods were of three days' duration, except the fore period in the case of the infant with tetany, which, because of the active symptoms manifested, had to be abbreviated to twenty-four hours. Information as to the cause of the acid effect from calcium chlorid ingestion was sought in the data obtained from the stools. The size of this effect was estimated by means of measurements made in the urine. Bicarbonate and chlorid concentrations in the plasma were determined with the purpose of obtaining, if possible, indication of the direct cause for the lowering of the former. The effect of calcium chlorid ingestion on the excretion of fixed alkali in the urine was also directly measured. The findings are given below in the order just indicated. The methods used in obtaining them were these: Sodium, potassium, calcium and magnesium were determined in blood serum, urine and stools by the methods of Kramer and Tisdall.[2] The bicarbonate of the plasma was measured by the method of Van Slyke.[3] For chlorids in the plasma a combination of Van Slyke's plan of precipitating the protein with picric acid and Volhard's thiocyanate

1. Holt and Howland (Diseases of Infancy and Childhood, New York, D. Appleton and Co., 1917) recommended from 30 to 60 grains (2 to 4 gm.) of calcium chlorid daily for control of the symptoms of tetany. The degree of the acid affect following the administration of calcium chlorid in usual doses may, therefore, be taken to be at least as large as was exhibited by these two infants.

2. Kramer, B.: J. Biol. Chem. **41**:263 (Feb.) 1920. Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **47**:475 (Aug.) 1921. Tisdall, F. F., and Kramer, B.: J. Biol. Chem. **48**: 1 (Sept.) 1921.

3. Van Slyke, D. D.: J. Biol. Chem. **30**:347 (June) 1917.

titration was used.[4] The procedure was essentially the same as that recently published by Myers and Short.[5] The p_H and titratable acidity of the urine were determined by the methods of Palmer and Henderson.[6] Ammonia was measured in the urine by the method of Folin and Macallum [7] and urine nitrogen by the usual Kjeldahl method.

THE CAUSE OF THE ACID EFFECT FOLLOWING CALCIUM CHLORID INGESTION AS INDICATED BY DATA OBTAINED FROM STOOL ANALYSES

The measurements of calcium and of chlorid found in the stools are given in Table 1. Since in this study we are concerned with the calcium ion (Ca^{++}) as the base and with the acid value of the chlorid ion (Cl^{-}), the amounts found have been expressed as cubic centimeters of tenth normal acid or base; e. g., the values given for calcium indicate the number of cubic centimeters of a tenth normal solution of base

TABLE 1.—*Measurements of Calcium and of Chlorid in Stools: Values for Each Twenty-Four Hours*

	Infant W., Normal		Infant H., Tetany	
	Ca C.c. N/10	Cl^- C.c. N/10	Ca C.c. N/10	Cl^- C.c. N/10
Added to milk, $CaCl_2$ period	365	365	270	270
Found in stools, $CaCl_2$ period	492	31	418	94
Fore period	272	17	166	9
From added $CaCl_2$	220	14	252	85
Per cent. from added $CaCl_2$	60	4	98	32

Estimated Cl metabolized without Ca.....Infant W. 207 — 14 = 193 c.c. N/10
From added $CaCl_2$.....Infant H. 252 — 85 = 167 c.c. N/10

which could be obtained from the amounts of calcium found. That there is actually a very much larger excretion of calcium than of chlorid from ingested calcium chlorid is shown in the table. Estimated by subtracting the amount of calcium found in the stools during the fore period from the amount found when calcium chlorid was given, 60 per cent. of the added calcium was excreted in the stools in the case of the normal infant. In contrast, estimated in the same way, only 4 per cent. of the added chlorid escaped absorption. With the 220 c.c. of tenth normal calcium from added calcium chlorid there appears in the stools but 14 c.c. tenth normal chlorid. It is, therefore, evident that other base than calcium was used in the metabolism of 220 — 14 = 206 c.c. tenth normal of the 365 c.c. tenth normal chlorid given. It cannot be assumed that 206 c.c. of tenth normal of the

4. The method used was an unpublished one devised by Dr. Dana W. Atchley.

5. Myers, V. C., and Short, J. J.: J. Biol. Chem. **44**:47, 1920.

6. Palmer, W. W., and Henderson, L. J.: Arch. Int. Med. **12**:153, 1913.

7. Folin, O., and Macallum, A. B.: J. Biol. Chem. **11**:523, 1912.

added chlorid was absorbed without calcium. Doubtless a part of the calcium represented by this value was absorbed and then excreted through the wall of the lower intestine. Since, however, this part does not carry chlorid with it into the stools, it may correctly be included in the calcium, measuring the extent to which absorbed chlorid is left to bind other base in the body fluids. The value thus found, 206 c.c. of tenth normal, it will be seen is more than half of the administered chlorid (365 c.c. of tenth normal). In the case of the infant with tetany (Infant H.), the ingestion of calcium chlorid resulted in the production of loose stools and in consequence a much larger proportion of the ingested calcium and also of chlorid appeared in the stools (Table 1). The estimated chlorid conveyed through the body fluids and excreted without calcium was, in this instance, $252 - 85 = 167$ c.c. tenth normal, again more than half of the chlorid (270 c.c. tenth normal) placed in the milk.

ESTIMATION OF THE ACID VALUE OF INGESTED CALCIUM CHLORID BY MEANS OF DATA OBTAINED FROM THE URINE

If the excess of the chlorid ion over the calcium ion absorbed were the only consequence of the addition of calcium chlorid to the food, the just estimated values for this excess could be taken as measurements of the acid effect of the calcium chlorid ingested. They would indicate that the calcium chlorid administered to these infants was, from the point of view of acid-base metabolism, an acid substance to the extent of more than half of its equivalence as hydrochloric acid. It is hardly likely, however, that other values for acid and base absorbed would be unaffected by calcium chlorid ingestion. The probability, for instance, that the absorption of phosphoric acid would be lowered as a consequence of an increased formation of insoluble calcium phosphates in the intestine has been mentioned. A measurement of the actual extent of the acid effect of calcium chlorid is best obtained by noting in the urine the extension of those factors whose purpose it is to cover an increase in the metabolism of acid as compared with that of fixed alkali.[8] Henderson[9] and Henderson and

8. The term "fixed alkali" is used to distinguish the bases which are contained preformed in the food; viz., sodium, potassium, calcium and magnesium, from the base ammonia which is derived from the metabolism of protein. Although ammonia is derived from organic substances, it may not, since it does not contain carbon, be correctly called an organic base. This fact makes it necessary to use the terms fixed alkali and ammonia, rather than inorganic and organic base, in describing the metabolism of the base. The differentiation of ammonia from fixed alkali is important from the point of view of acid-base metabolism, for the reason that ammonia is biologically a toxic ion and cannot be used to appreciable extent as a base within the body, and in consequence the base concentrations of the body fluids must be composed practically entirely of fixed alkali.

9. Henderson, L. J.: Am. Physiol. **21**:427, 1908; J. Biol. Chem. **9**:403, 1911.

Palmer [10] have shown that the extent to which acids are permitted to carry fixed alkali into the urine is controlled by (1) a regulation of the acidity of the urine, and (2) a regulated production ammonia. By the operation of these two factors of acid excretion, the base concentration of the plasma, which must be practically entirely fixed alkali, is sustained at a constant level. The necessity for this regulatory function of the kidney is indicated by the fact that even though the diet is a usual one, the quantity of acid substances claiming excretion in the urine is much larger than the intake of fixed alkali. It has been shown that this regulatory mechanism is widely extensible and will manage the excretion of large additions to the acid excretion without lowering of the base concentration in the plasma (Gamble, Ross and Tisdall [11]). Henderson [9] and Henderson and Palmer [10] have shown that a measurement of the titratable acidity of the urine plus the ammonia excretion measures the excess of acid excretion over fixed alkali excretion. The sum of these two measurements they have designated "total acid," i. e., that part of

TABLE 2.—*Increase in Ammonia in the Urine Following Calcium Chlorid Ingestion*

	Ammonia in Urine			
	Fore Period, Average 24 Hours, C.c. N/10	$CaCl_2$ Period		
		1st Day, C.c. N/10	2d Day, C.c. N/10	3d Day, C.c. N/10
Infant W. (normal)	116	194	275	306
Infant H. (tetany)	53	104	141	180

the acid excretion which has been accomplished without an expenditure of fixed alkali. Addition to the food of a substance increasing the discrepancy between the amount of acid claiming excretion and the amount of fixed alkali available for binding it in the urine should cause an equivalent extension of this "total acid" value in the urine. By the use of this principle we have undertaken to measure the acid effect of ingested calcium chlorid, using the values found for titratable acidity of the urine and ammonia excretion during the fore period as a basis from which to measure the extension of these values when calcium chlorid was given.

Ammonia, much the larger of the two factors conserving inorganic base, was determined in the urines day by day. The values found (Table 2) indicate very clearly that ingested calcium chlorid is, from the point of view of acid-base metabolism, an acid substance. Ammonia being derived at the expense of the neutral end-product of protein

10. Henderson, L. J., and Palmer, W. W.: J. Biol. Chem. **17**:305, 1914.
11. Gamble, J. L.; Ross, S. G., and Tisdall, F. F.: Tr. Am. Ped. Soc. **34**:289, 1922.

metabolism, urea, an extension of the ammonia factor can be well shown by noting the increasing proportion of the total urine nitrogen which is ammonia nitrogen, when, as in this case, the metabolism of protein remains a stationary value. This often used index of the degree of an acid effect, the "ammonia coefficient," is given in Table 3. These data are from the normal infant (W.) and will satisfactorily indicate that in terms of the "ammonia coefficient" the acid effect following calcium chlorid ingestion may be designated as large.

In Table 4 are given the measurements of urinary acidity and ammonia excretion and the sum of these measurements, "total acid," found for the fore and calcium chlorid periods. Subtracting the values

TABLE 3.—*Increase in "Ammonia Coefficient" Following Calcium Chlorid Ingestion in the Case of Infant W. (Normal)*

	Fore Period, Average 24 Hours	$CaCl_2$ Period		
		1st Day	2d Day	3d Day
Total nitrogen, gm.	1.61	1.67	1.72	1.69
Ammonia nitrogen, gm.	0.16	0.27	0.39	0.43
Percentage ratio of ammonia nitrogen to total nitrogen	10	16	22	25

TABLE 4.—*Extension of the Factors Regulating Fixed Alkali Excretion Following Calcium Chlorid Ingestion: Values for Each Twenty-Four Hours*

Subject		p_H	Values for Each 24 Hours		
			Titratable Acidity, C.c. N/10	Ammonia, C.c. N/10	Total Acid, C.c. N/10
Infant W. (normal)	$CaCl_2$ period	5.5	67	258	325
	Fore period	6.2	58	116	174
	Increase		9	142	151
Infant H. (tetany)	$CaCl_2$ period	5.3	54	143	197
	Fore period	5.5	45	53	98
	Increase		9	90	99

for the fore period from those found when calcium chlorid was given, measurements of the extension of these values and of their sum are obtained. Provided the kidney has accurately carried out its regulatory function, the increase in "total acid" should measure the increase in the excess of acid claiming excretion over available fixed alkali caused by adding calcium chlorid to the food; i. e., the acid effect following ingestion of this neutral salt. As may be seen in the table, the acid value of the ingested calcium chlorid was found to be 151 c.c. tenth normal, and 99 c.c. tenth normal, for the normal infant and the infant with tetany, respectively. These values are considerably less than those obtained for the excess of chlorid over calcium metabolized obtained from the stool analyses (Table 1); namely, 193 c.c. tenth normal and 167 c.c. tenth normal. Nevertheless, they indicate that a

very considerable part of the chlorid given as calcium chlorid was metabolized in the same way as would have been the case if placed in the food as hydrochloric acid. The acid equivalence of the calcium chlorid given may be estimated as $\frac{151}{365} = 0.41$ in the case of the normal infant, and for the infant with tetany as $\frac{99}{270} = 0.37$. In other words, calcium chlorid was, from the point of view of the acid-base metabolism of these infants, an acid substance to the extent of about 40 per cent. of its equivalence as hydrochloric acid.

THE DIRECT CAUSE OF THE LOWERING OF THE SERUM BICARBONATE FOLLOWING CALCIUM CHLORID INGESTION AS INDICATED BY DATA OBTAINED FROM THE BLOOD SERUM

In obtaining the foregoing estimate of the acid value of ingested calcium chlorid, the premise is used that the regulatory function of the kidney has been accurately operative in sustaining the normal total base (fixed alkali) concentration of the serum. Direct test of the

TABLE 5.—*Measurements of Fixed Alkali in Blood Serum from Infant H, Before and After Calcium Chlorid Ingestion*

	Before $CaCl_2$ Period, C.c. N/10 per 100 C.c.	At End of $CaCl_2$ Period, C.c. N/10 per 100 C.c.
Sodium	139.0	138.2
Potassium	6.1	5.6
Calcium	2.6	4.0
Magnesium	1.5	0.9
Total base	149.2	148.7

accuracy of the regulation of fixed alkali excretion may be made by measuring the total concentration of fixed alkali in the blood serum. This measurement involves separate determinations of the four bases, sodium, potassium, calcium and magnesium. The recently devised methods of Kramer and Tisdall makes this a feasible project. The four measurements were made in the case of Infant H. before and after the administration of calcium chlorid, and the data obtained are given in Table 5, the values being expressed as cubic centimeters tenth normal base per hundred cubic centimeters of blood serum. The sum of the four values before and after calcium chlorid administration are approximately the same, their agreement being well within the limits of error (taken to be $\pm$ 4 per cent.) in obtaining a measurement of the total base in this way.

The significance of these data is that the metabolism of extra acid from calcium chlorid has not disturbed the concentration of the total base in the blood serum. It is, therefore, not possible to explain a lowering of bicarbonate concentration in the serum, following calcium chlorid ingestion, as a consequence of decrease in the concentration of the base. There was found, nevertheless, a marked lowering of the

bicarbonate concentration in the serum in the case of both the normal infant and the infant with tetany following administration of calcium chlorid. The extent of this lowering is seen in Table 6; 24 per cent. and 21 per cent., respectively, in the case of the normal infant and of the infant with tetany. Since it is impossible to explain this decrease in bound carbonic acid as a consequence of base loss from the serum, there remains the possibility that an increase in the concentration of acid substance (or substances) has replaced a part of the bound carbonic acid. The acid value which might be expected to rise in the blood serum following calcium chlorid ingestion is obviously the chlorid ion concentration. Measurements of the chlorid concentration in serum samples from Infant H. (tetany) before and after giving

TABLE 6.—*Measurements of Bicarbonate Concentration in Serum Before and After Calcium Chlorid Ingestion*

	Infant W. (normal), per Cent. of Bound Carbon Dioxid by Volume	Infant H. (tetany), per Cent. of Bound Carbon Dioxid by Volume
Before $CaCl_2$	54.1	50.4
After $CaCl_2$	40.9	40.0
Decrease	13.2	10.4
Percentage of decrease	24	21

TABLE 7.—*Comparison of Chlorid Increase with Bicarbonate Reduction in Serum from Infant H., Before and After Calcium Chlorid Ingestion*

	Cl^-,* C.c. N/10 per 100 C.c. Serum	HCO_3^-, C.c. N/10 per 100 C.c. Serum
Before $CaCl_2$	106	23
After $CaCl_2$	112	18
	+6	−5

* Chlorids as grams NaCl per thousand cubic centimeters: Before $CaCl_2$, 6.13 gm.; after $CaCl_2$, 6.58 gm.

calcium chlorid showed a very considerable rise in the chlorid concentration of the serum at the end of the calcium chlorid period; from 6.13 to 6.53 gm. as sodium chlorid per liter. The increase in bound hydrochloric acid was, moreover, approximately equivalent to the decrease in bound carbonic acid. The lowering of bicarbonate in the case of this infant is thus adequately explained by a rise in chlorid concentration, and assumption of a loss of the base from the serum is, therefore, not required. The data demonstrating this point are given in Table 7.

In order further to illustrate the manner in which increase of chlorid in the serum may be expected to diminish the concentration of bound carbonic acid, assuming that the total base remains stationary, the diagrams in Figure 1 were prepared. The left side of

each of the diagrams represents the total base concentration, expressed as cubic centimeters tenth normal base per hundred cubic centimeters of serum, as determined by the four measurements given in Table 5. On the right side of the diagram, the values for the acids which bind the base in the plasma are indicated. Beginning at the top, and using the measurements given in Table 7, the concentrations of bicarbonate (HCO_3^-) and then of chlorid (Cl^-) are laid off. The sum of the usual concentrations of three other acids known to be carried in the plasma, phosphoric, sulphuric and certain organic acids, is indicated by the small block below the measurement of the chlorid (Cl^-) concentration.[12] After laying off the directly measured values for bicarbonate (HCO_3^-) and chlorid (Cl^-) and an assumed average value for the other three acids, there remains a portion of the base in the plasma in excess of the sum of these values. It is a reasonable surmise that this remainder of the total base is bound by the plasma proteins. At the reaction of blood plasma the proteins may correctly be regarded as acid substances. The diagrams indicate fairly completely the character of the acid-base composition of the plasma. It may be noted that four of the acids in the plasma, hydrochloric, phosphoric, sulphuric and the organic acids, are being conveyed for excretion in the urine and that one of them, hydrochloric acid, is carried at a comparatively huge concentration covering nearly three fifths of the total base of the plasma. This fact is striking when it is remembered that, diet being a usual one, a twenty-four hour urine specimen contains approximately the same amount of each of these four acids. The other two acid values, bicarbonate (HCO_3^-) and protein, do not under normal circumstances enter the urine. Remaining in the plasma they have to do with stabilizing the reaction of the blood. As regards the character of the base in blood plasma, the fact that it is practically entirely fixed alkali may be illustrated by stating that the concentration of ammonia in blood plasma would be approximately represented by the thickness of the line at the top of the diagram. In contrast to this minute concentration in the

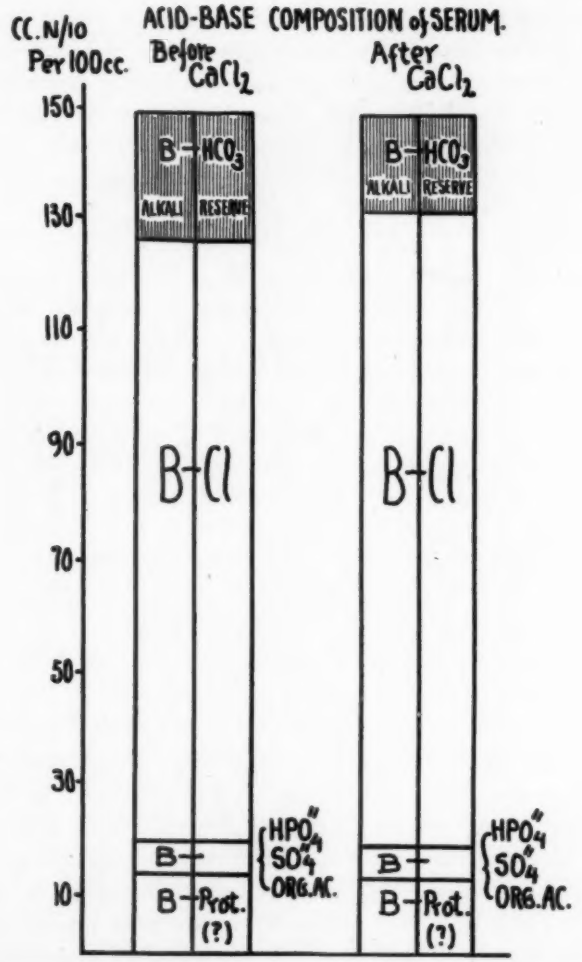
12. The base bound in the plasma by the usual concentrations of the normal phosphate ion ($HPO^=$), of the sulphate ion ($SO_4^=$) and organic acids together is here taken as 6 c.c. tenth normal per hundred cubic centimeters of plasma. From published data the base bound as phosphate may be taken as 2.3 c.c. tenth normal per hundred cubic centimeters, and as sulphate as 1.7 c.c. tenth normal per hundred cubic centimeters. The concentration of the organic acids normally present in the plasma has not been accurately measured. Attempts at such a measurement in this laboratory by one of the authors (Ross), although unsatisfactory from the point of view of a sufficient accuracy, at least indicate that this concentration is a very small one. On this premise it has been assigned 2 c.c. tenth normal per hundred cubic centimeters. It may also be noted here that the base equivalence of the normal phosphate (HPO_4) per molecule indicated in the accompanying chart as 2 is actually, according to Sörensen's data, 1.8 at the usual reaction of blood plasma.

plasma is the fact that under usual conditions, as regards diet, from one third to one half of the base in urine is found to be ammonia. There is thus indicated the fact that the sum of the acid substances derived from a usual diet and claiming excretion in the urine is much in excess of the intake of fixed alkali, and the necessity for a regulated use of ammonia in the excretion of these acid substances in order that the base in the plasma may be sustained is apparent. The manner of the effect of an increase in the concentration of chlorid (Cl^-) on the bicarbonate (HCO_3^-) of the plasma may now, with the help of these diagrams, be briefly indicated. This effect is a consequence of the peculiar character of the concentration of bound carbonic acid, which may be described by stating that the block on the right side of the diagram indicating bound carbonic acid is automatically adjustable and will change in size following alteration of any of the other values indicated in the diagram. This adjustability is due to the fact that carbonic acid is an extremely weak acid, and also that in the plasma there is an approximately sustained level of free carbonic acid. In consequence, loss of the base will be at the expense of bicarbonate; increase of a stronger acid will obtain base from bicarbonate, and, on the other hand, if, by any means, the amount of base available for use as bicarbonate is increased it will at once be bound by the free carbonic acid.[13]

In this instance, as is illustrated in the diagram, the reduction of bicarbonate is a consequence of an increase in chlorid (Cl^-), the base remaining stationary. The fact that total base was found to remain stationary is a point of considerable physiologic significance. Obviously, a decrease in bicarbonate could be compensated for by an increase in the base concentration. Apparently, however, the mechanism regulating fixed alkali excretion serves primarily the purpose of maintaining a constant level of the base in the serum and does not raise this level in behalf of a diminished bicarbonate. In other words, the regulatory function of the kidney is not, as is often inferred, directly in support of the "alkali reserve." The maintenance of a constant level of total base is thus indicated as a matter of greater importance than maintenance of the bicarbonate concentration at its usual size. The necessity for a

13. In this discussion the adjustability of the acid side of the accompanying chart to the base level is attributed entirely to the elasticity of the bicarbonate concentration. This is practically the case. It should be mentioned, however, that the phosphate and proteinate values (in terms of base bound) are not to be regarded as immovable in the presence of strong acids claiming base. Secondary phosphate and the proteinates being salts of weak acids will tend to supply the base at the expense of a shift in reaction due to release of acid phosphate and protein. In the case of bicarbonate the tendency to shift of reaction is rapidly offset by removal of carbonic acid by way of the lungs. It is owing to this fact chiefly that bicarbonate supplies nearly all of the base for neutralization purposes; i. e., it practically constitutes the "alkali reserve."

constancy of the total base concentration is understandable from the fact that, owing to the adjustability of the value for bound carbonic acid, it is the size of the base concentration which determines the total salt content of the plasma. The osmotic pressure of the plasma may, therefore, be said to be closely dependent on the mechanism sustaining



Acid-base composition of blood serum from Infant H. before, and the third day following, calcium chlorid administration. Constructed from measurements of base given in Table 5 and of chlorin and bicarbonate in Table 7, to illustrate reduction of the alkali reserve caused by increase in the chlorid (Cl^-) concentration.

the base concentration. It is difficult to imagine means of extensive compensation for the effect on osmotic pressure of alterations in the base concentration. The relatively less necessity for a constancy of bicarbonate concentration is understandable because of the known

extensibility of the other factors concerned in neutrality regulation (circulatory and respiratory) in compensation for a lowered alkali reserve.

THE SIGNIFICANCE OF AN INCREASED EXCRETION OF FIXED ALKALI IN THE URINE FOLLOWING CALCIUM CHLORID ADMINISTRATION

The measurements of the total base in the blood serum from Infant H. given above constitute evidence that the excretion of the extra acid when calcium chlorid was given was managed without appreciable depletion of the base concentration of the body fluids. In making this statement the premise is used that a normal concentration of the base in the serum may be taken to indicate that the concentrations

TABLE 8.—*Excretion of Inorganic Base Before and Following Calcium Chlorid Ingestion: Values for Each Twenty-Four Hours*

Base	Infant W.		Infant H.	
	Fore Period, C.c. N/10	$CaCl_2$ Period, C.c. N/10	Fore Period, C.c. N/10	$CaCl_2$ Period, C.c. N/10
Urine:				
Sodium	55.2	84.8	14.7	99.1
Potassium	103.0	110.0	110.0	96.4
Magnesium	1.2	3.4	2.5	5.0
Calcium	2.8	17.5	4.0	4.5
Total	162.2	215.7	131.2	205.0
Increase	.....	53.5	.....	73.8
Stools:				
Sodium	16.1	20.0	4.4	43.5
Potassium	40.0	62.0	19.7	49.5
Magnesium	22.5	46.7	22.5	35.0
Calcium	272.0	492.0	166.0	418.0
Total	350.6	620.7	212.6	546.0
Increase	.....	270.1	.....	333.4
Total excretion	513	836	343	751
Total increase	...	324	...	408
Base added (calcium)	...	365	...	270

of base in other inaccessible portions of the body water cannot be greatly altered. In apparent contradiction of this inference from the base measurements in the serum, there was found in the urine from both infants a moderately large increase in fixed alkali excretion during the calcium chlorid periods. This extra base includes, only in the instance of Infant W., and to a very slight extent, the base calcium which was added to the intake. The size and composition of this increased base excretion in the urine are shown in Table 8. The table also includes measurements of the base contained in the stools, and it will be seen that the amounts are larger for each of the four bases during the calcium chlorid periods. The increased excretion chiefly of sodium and potassium in the urine was, therefore, not a consequence of an increased absorption. Does this large increase in fixed alkali excretion in the urine measure a failure of the kidney to sustain correct base concentrations in the body fluids? Were it permissible to assume that the

volume of body water remained the same during the two experimental periods, such an inference would be unavoidable. It is a nearly certain premise, however, that the ingested calcium chlorid would exert a diuretic effect, with consequent decrease in the volume of body water. A reduction of body water would provide a quantity of inorganic base for use in the process of acid excretion without disturbance of the base concentrations in the remaining body fluids. With the evidence from Infant H. of a correctly sustained base level in the serum, it would seem reasonable to regard the increased base excretion as probably entirely a consequence of the diuretic effect of calcium chlorid. As indication that there was probably a considerable loss of body water, the increase in volume of urine during the calcium chlorid periods may be noted. During the fore period of Infant W., the average twenty-four hour volume of urine was 420 c.c., and during the calcium chlorid period this value was found to be 510 c.c. Infant H. voided only 270 c.c. the day before calcium chlorid administration. The average twenty-four hour urine volume for the three following days was 390 c.c. This large increase in the volume of urine is especially significant since it occurred in the presence of a considerable loss of water in the stools.[14] In definite agreement with the postulation of a loss of body water during the periods of calcium chlorid administration, losses in body weight were in both instances measured, Infant W. losing 90 gm., and Infant H., 300 gm.

As an objection to the inference of a loss of body water in explanation of the increased excretion of sodium, potassium and magnesium, it might be argued that the increased excretion of these bases was offset by an increased retention of the added base calcium. It may, indeed, be derived from the data in Table 8 that in the case of Infant W. the increased retention of calcium was larger than the combined increase in excretion of the three other bases. This increase in calcium retention may be estimated by subtracting the increase in excretion from the calcium added to the milk, thus, from Table 8, $510 - 275 = 235$ c.c. tenth normal increase in excretion of calcium when calcium chlorid was given. Subtracting this value from the 365 c.c. tenth normal calcium added to the intake during this period, 130 c.c. tenth normal calcium is indicated as the increase in calcium retention following calcium chlorid administration. The increased excretion of the other three bases was $327 - 238 = 89$ c.c. tenth normal and was, therefore, more covered by the

14. The stools of Infant H. (tetany) were, during the fore period, small in amount, formed and dry. During the calcium chlorid period they became definitely diarrheal in character and contained 140 c.c. of water each twenty-four hours. The stools of Infant W. (normal) contained rather more than a usual amount of water, during both the fore and the experimental periods, their water content for each twenty-four hours being 70 c.c. and 110 c.c., respectively, during the two periods.

increased retention of calcium. It would be almost certainly incorrect, however, to assume that the retained calcium replaced in the body water the lost sodium, potassium and magnesium. Calcium being held at a constant and relatively very small concentration, it is scarcely likely that in this normal infant this level would be raised. In all probability the extra calcium retained was added to the calcium deposits of the body. In the case of Infant H., owing largely to the loose stools, the increase in the excretion of sodium, potassium and magnesium (155 c.c. tenth normal) was greatly in excess of the slight increase in calcium retention (17 c.c. tenth normal). Insomuch as sodium, potassium and magnesium, in contrast to calcium, are presumably present in the body entirely in solution in the body water, it seems reasonable to infer a reduction of the volume of body water from an increased excretion of these bases, provided evidence can be found, as in this instance, indicating that base concentrations in the body fluids have been correctly sustained. We are thus led to conclude that the acid effect of calcium chlorid; i. e., the increase in the excess of acid over fixed alkali claiming excretion, is probably entirely covered (and completely measured) by the increase in the titratable acidity of the urine, together with the increased ammonia excretion, and that the extra base found in the urine is a consequence of reduction of the volume of body water and does not represent depletion of base concentration within the body. The indicated ability of the kidney to sustain a constant base concentration in the body fluids under circumstances causing both a large alteration in the excess of acid over base claiming excretion and a considerable change in the volume of body water is worth admiring.

The importance of taking into account in any study of the metabolism of inorganic substances the possibility of alterations of the volume of body water is, we believe, worth emphasizing. Particularly in the case of sodium, potassium, chlorid and phosphate,[15] because of the high concentrations at which these ions are held in the body fluids, a marked alteration of the amounts eliminated will be a necessary consequence of relatively slight changes in the volume of body water. That fluctuation of this value is not an improbability is indicated by the irregularities of the day to day weight curve of a normal infant. In the case of malnourished infants these irregularities are often of such size as must very greatly effect the amounts of inorganic substances eliminated. That

15. The conspicuous size of the chlorin concentration may be seen in the accompanying chart. The even larger concentration of sodium may be indicated by the statement that it constitutes 92 per cent. of the base in blood plasma. Katz' (Arch. f. d. ges. Physiol. **63**:18, 1896) measurements of the inorganic constituents of fresh human muscle demonstrate that potassium is the chief base in muscle water and also indicate a considerable concentration of phosphates in this compartment of body water.

this factor will largely determine the excretion of inorganic substances, especially those mentioned above, following ingestion of unusual amounts of various salts, would seem to be altogether probable. It is our impression that many of the data obtained to represent the metabolism of the minerals have been incorrectly interpreted from failure to take into account the possibility of alterations of the volume of body water. Particularly do we wish to emphasize the incorrectness of inferring an alteration of concentrations within the body from the finding of an increase or decrease in elimination.

CONCLUSIONS

The following conclusions as regards the effect of calcium chlorid ingestion on acid-base metabolism are offered with the reservation that they rest upon data obtained from but two infants.

Ingested calcium chlorid in consequence of the relatively much greater absorption of the chlorid ion (Cl^-) than the calcium ion (Ca^{++}) behaves as does an acid substance. The effect on acid-base metabolism of the ingestion of 1 gm. of calcium chlorid may be described as of the same extent as would be produced by placing in the milk 75 c.c of tenth normal hydrochloric acid. The considerable increase in the excess of acid over fixed alkali claiming excretion in the urine is apparently accurately compensated for by an increase in urinary acidity and of ammonia excretion, with the result that the normal base concentration of the blood plasma is sustained. The lowering of bicarbonate following calcium chlorid ingestion is, therefore, not a consequence of depletion of the plasma base. It is found to be due to a rise in chlorid (Cl^-) concentration, displacing an equivalence of bound carbonic acid.

Following calcium chlorid ingestion there occurs a moderately large increase in the excretion of fixed alkali, especially of sodium and potassium in the urine. This is correctly to be regarded as a consequence of a reduction of the volume of body water, and not as indicating withdrawal of base from body fluids.

The total base concentration of the serum is sustained at a constant level by a remarkably accurate regulation of fixed alkali excretion in the urine. This regulation is successfully accomplished in the presence both of a large increase in the excess of acid over base claiming excretion and of a considerable change in the volume of body water. It is to be noted, moreover, that the normal total base concentration is not altered in behalf of a lowered bicarbonate.

STUDIES OF TETANY

II. THE EFFECT OF INGESTION OF HYDROCHLORIC ACID PRODUCING SUBSTANCES ON THE ACID-BASE METABOLISM OF AN INFANT AND THE PROBABLE MANNER OF THEIR ACTION IN THE TREATMENT OF TETANY *

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The data presented in this paper were obtained from an infant with tetany who was given, at intervals, ammonium chlorid, hydrochloric acid, the usual agent, calcium chlorid, and calcium acetate, a substance differing from the other three in that presumably it does not produce an acid effect. The purposes of this study may be briefly indicated by the headings, which will be used in the following order in presenting and discussing the information obtained.

1. Evidence indicating that an acid effect, due to an increased metabolism of hydrochloric acid, following the administration of calcium chlorid, ammonium chlorid or hydrochloric acid is a factor in the therapeutic efficacy of these substances in tetany.

2. Data illustrating the regulated use of fixed alkali in the process of acid excretion.

3. The manner of the effect of an increased metabolism of hydrochloric acid on the excretion in the urine of other acid substances and of fixed alkali.

4. The manner of the effect of an increased metabolism of hydrochloric acid on the plasma bicarbonate.

5. The reaction of the plasma in the presence of an increased metabolism of hydrochloric acid.

6. The probable manner of a therapeutic effect in tetany following the administration of substances producing an increased metabolism of hydrochloric acid.

The infant upon whom this study was made was a fairly well developed and well nourished colored boy, 13 months old, weighing 19 pounds. He presented slight evidences of rickets, which were confirmed by roentgenographic examination. He entered the hospital with an acute otitis media, exhibiting at the same time marked manifestations of tetany. Occasional "spasms" had been noted during the month

* Received for publication, March 21, 1923.
* From the Department of Pediatrics, Johns Hopkins University, Baltimore.

preceding admission to the hospital. Following an incision of the right ear drum, the symptoms of an acute infection rapidly disappeared, but those of tetany persisted. For the first three days of his stay in the hospital, owing to the general symptoms from the acute otitis media, he was given as food only small amounts of diluted milk. Beginning the fourth day after admission and continuing throughout the long period of observation (nearly eight weeks), the food given was a liter of whole milk each day, with the addition, during the last ten days of his stay in the hospital, of cod liver oil, orange juice and farina.

1. EVIDENCE INDICATING THAT AN ACID EFFECT, DUE TO AN INCREASED METABOLISM OF HYDROCHLORIC ACID, FOLLOWING THE ADMINISTRATION OF CALCIUM CHLORID, AMMONIUM CHLORID AND HYDROCHLORIC ACID IS A FACTOR IN THE THERAPEUTIC ACTION OF THESE SUBSTANCES IN TETANY

Demonstration [1] that calcium chlorid, the agent most frequently used in the treatment of infantile tetany, behaves within the body to a large extent as an acid substance suggests that an acid effect caused by this substance may be a factor in its therapeutic action in tetany. An obstacle to this inference is the fact that the calcium content of the plasma is increased by the administration of calcium chlorid. The marked decrease in the calcium of the blood plasma, which is quite specifically characteristic of active tetany,[2] and the well founded probability of a relationship of the ionized fraction of the calcium in the body fluids to the control of neuromuscular irritability [3] make necessary the admission that the therapeutic action of calcium chlorid may be entirely a consequence of the increased calcium concentration which it causes. The possibility of an acid effect from this salt being also a factor in the therapeutic result can obviously best be tested by the administration of substances which may be expected to produce an acid effect of the same character as that produced by calcium chlorid, without, at the same time, raising the calcium content of the plasma. Since J. B. S. Haldane [4] has recently demonstrated that ammonium chlorid is metabolized to a large extent as hydrochloric acid, probably by reason of the ammonia being conveyed through the body fluids in the form of the neutral substance urea, this salt would seem to be exactly suitable for testing the possibility that the acid effect noted in the case of calcium chlorid administration is a factor in the relief of the symptoms of tetany. Pre-

1. Gamble, J. L., Ross, G. S., and Tisdall, F. F.: Studies of Tetany. I. The Effect of Calcium Chlorid Ingestion on the Acid Base Metabolism of Infants, Am. J. Dis. Child., this issue, page 455.

2. Howland, J., and Marriott, W. McK.: Quart. J. Med. **11**:289 (July) 1918.

3. Reiss, E.: Ztschr. f. Kinderh. **3**:1, 1911; MacCallum and Voegtlein: J. Exper. Med. **11**:118, 1909; Loeb, J.: J. Biol. Chem. **23**:423, 1915.

4. Haldane, J. B. S: J. Physiol. **55**:265 (Aug.) 1921.

sumably, the character of the acid effect produced by calcium chlorid and ammonium chlorid would be the same as would follow placing hydrochloric acid in the milk.

While we were proceeding to test the therapeutic value of the acid effect from calcium chlorid by the administration of ammonium chlorid and of hydrochloric acid to the subject of this study, papers by German investigators demonstrating the therapeutic action in tetany of both ammonium chlorid and hydrochloric acid came to hand. The point was quite thoroughly tested by Scheer,[5] using a "hydrochloric acid milk" and by Freudenberg and György[6] by the administration of ammonium chlorid. The data from the subject of this study are, as regards the therapeutic effect from the administration of either of these substances, in agreement with the much more extensive evidence presented by these workers. The data on this point are given in Table 1. It will be seen that the administration of ammonium chlorid and of hydrochloric acid caused a complete disappearance of the evidences of increased neuromuscular irritability. As regards the amounts of these substances given, it may be said that they are the equivalents, on the basis of chlorin content, of a fairly large dose of calcium chlorid.[7] Following the brief periods of administration, there occurred, in both instances, an almost immediate reappearance of the manifestations of active tetany. It is to be noted that the ingestion of hydrochloric acid was followed by an increase in the calcium content of the blood serum and that this increase was approximately of the same magnitude as followed the administration of calcium chlorid in an amount equivalent on the basis of chlorid (Cl^-) content. This effect from hydrochloric acid is doubtless due to an increased absorption of calcium as calcium chlorid produced in the milk at the expense of the dicalcium and tricalcium phosphates. This point was appreciated by Scheer,[5] and he assumed correctly that the placing of hydrochloric acid in milk would

5. Scheer, K.: Jahrb. f. Kinderh. **97**:130 (Feb.) 1922.

6. Freudenberg, E., and György: Klin. Wchnschr. **1**:410 (Feb. 25) 1922.

7. The dose of calcium chlorid for each twenty-four hours, usual in the treatment of tetany, is from 2 to 4 gm. The 4 gm. calcium chlorid given this infant contains of chlorin, 2.6 gm., or 730 c.c. tenth normal. Of this, 40 per cent. (290 c.c. tenth normal) may, on the basis of the data given in the preceding paper (Footnote 1), be regarded as hydrochloric acid. The 4 gm. of ammonium chlorid given also provides an intake of 2.6 gm. of chlorin or 730 c.c. tenth normal, all of which, however, as will appear in this paper, is probably metabolized as hydrochloric acid. In demonstrating the therapeutic efficacy of this salt Freudenberg and György gave from 3 to 6 gm. The hydrochloric acid given was in terms of normality, 750 c.c. tenth normal; i. e., approximately the same amount as was assumed to be derived from 4 gm. ammonium chlorid. This is a several times larger dose than was used by Scheer, 260 c.c. tenth normal. It is of interest to note that the amount of hydrochloric acid which Scheer gave corresponds roughly to the estimated hydrochloric acid production from 4 gm. of calcium chlorid (compare the foregoing).

in this indirect manner bring about an increase in the calcium content of serum. It is apparent, however, that this fact obstructs the inference that an acid effect from hydrochloric acid ingestion is also a factor in the therapeutic result. On this point, however, the evidence is clear in the case of ammonium chlorid. It may be seen in the table that there occurred an actual diminution of the calcium content of the serum during the period of ammonium chlorid administration. The absence

TABLE 1.—*Therapeutic Effect in Tetany of the Administration of Ammonium Chlorid and Hydrochloric Acid*

Date	Treatment	Electrical Reactions		Ca in Blood Serum, Mg. per 100 C.c.	Clinical Signs of Tetany
		Anodal Opening, Milliamperes	Cathodal Opening, Milliamperes		
May 2	.....	2.8	4.4		
May 3	.....	2.4	4.4		
May 6	NH_4Cl 4 gm.	1.8	3.0	7.1	
May 7	NH_4Cl 4 gm.	3.4	>5.0	...	Chvostek sign present
May 8	NH_4Cl 4 gm.	>5.0	>5.0	6.9	
May 9	.....	>5.0	>5.0	6.4	Chvostek sign not present
May 10	.....	2.4	3.0	...	Chvostek sign marked
May 11	$CaCl_2$ 4 gm.	2.2	3.8	5.2	Chvostek sign, laryngeal stridor
May 12	$CaCl_2$ 4 gm.				
May 13	$CaCl_2$ 4 gm.	4.8	>5.0	8.0	Slight Chvostek sign
May 14	.....	>5.0	>5.0	...	No Chvostek sign
May 15	.....	2.8	4.0	...	Chvostek sign present
May 16	.....	1.8	2.4	5.0	Chvostek sign, laryngeal stridor
May 17	.....	.....	3.0		
May 18	Ca acetate 5.0 gm.				
May 19	Ca acetate 6.3 gm.	2.4	4.4		
May 20	Ca acetate 6.3 gm.	3.2	>5.0	6.6	
May 21	.....	>5.0	>5.0	...	Slight Chvostek sign
May 22	.....	2.2	4.6		
May 24	Ca acetate 6.3 gm.	1.8	3.6	5.9	
May 25	Ca acetate 6.3 gm.	2.2			
May 26	Ca acetate 6.3 gm.	1.6	>5.0		
May 27	Ca acetate 6.3 gm.	1.4	>5.0		
May 28	.....	3.4	>5.0	6.9	Chvostek sign slightly positive
May 29	.....	2.0	>5.0		
June 5	HCl 2.72 gm.*	.....	.....	5.0	Cathodal closure tetanus below 5 milliamperes
June 6	HCl 2.72 gm.*.....	>5.0	>5.0		
June 7	.....	>5.0	>5.0	7.6	Slight Chvostek sign
June 8	.....	>5.0	>5.0		
June 9	.....	2.8	>5.0	...	Marked Chvostek sign
June 10	Cod liver oil, farina and orange juice	2.8	>5.0	5.6	
June 17	Cod liver oil, farina and orange juice	>5.0	>5.0	...	Chvostek sign just obtainable
June 20	Cod liver oil, farina and orange juice	.....	.....	...	No Chvostek sign
June 24	Cod liver oil, farina and orange juice	>5.0	>5.0	9.7	No Chvostek sign

* Obtained by placing 75 c.c. tenth normal HCl in milk.

of an augmenting effect on the calcium content of the serum following ammonium chlorid ingestion is understandable; hydrochloric acid being presumably derived from this salt only after it is absorbed and thus too late to bring about an increased absorption of calcium as calcium chlorid. The fact demonstrated by Freudenberg and György [6] that the ingestion of ammonium chlorid will relieve the symptoms of tetany may, therefore, be taken as clearly indicating a process which is independent of the size of the calcium concentration in the serum. The outstanding consequence of ingesting ammonium chlorid is a large

increase in the metabolism of hydrochloric acid. It would, therefore, seem highly probable that the therapeutic action of ammonium chlorid is in some way a result of an alteration of acid-base values caused by metabolism of an unusually large amount of hydrochloric acid, and that calcium chlorid or hydrochloric acid placed in the milk will exert an effect identical in this respect with that following the ingestion of ammonium chlorid.

As indirect evidence that an acid effect may be a factor of importance in relieving the symptoms of tetany may be cited the fact obtained from clinical experience that calcium chlorid has a greater therapeutic efficacy than calcium acetate. The acid portion of the latter being oxidizable, ingestion of this salt would not be expected to exert an effect on the acid-base values within the body. We noted, with F. F. Tisdall,[1] a reduction of the plasma bicarbonate following the ingestion of calcium chlorid. Measurements of the plasma bicarbonate were obtained from the subject of this study two days and again four days after beginning calcium acetate therapy. The values found were 53.2 and 51.3 per cent. of carbon dioxid bound by volume; i. e., not appreciably less than the usual value. It may also be noted as regards the comparative efficacy of this salt that it produced a much less marked rise in the calcium content of the serum than did calcium chlorid, presumably indicating a better absorption of calcium chlorid. The amount of calcium given as calcium acetate was the same as was contained in the calcium chlorid given. It is interesting to note that hydrochloric acid produced a greater rise in the calcium content of the serum than did the calcium containing salt (calcium acetate).

It is worth noting that following cessation of the administration of the agents used there was, in every instance, a prompt recurrence of the manifestations of tetany. The impression is obtained that these agents resist rather than remove the underlying cause of the tetany. Following the reappearance of symptoms after the hydrochloric acid period, the infant was given cod liver oil, orange juice and farina. On this mixed diet the evidences of tetany soon disappeared, and did not recur during the remainder of his stay in the hospital. The effect of these additions to the diet must be in its manner quite different from that of the hydrochloric acid producing substances, and probably may be regarded as, in a correct sense, curative.

2. DATA ILLUSTRATING THE REGULATED USE OF FIXED ALKALI IN THE PROCESS OF ACID EXCRETION

Since the administration of calcium chlorid, ammonium chlorid or hydrochloric acid amounts, from the point of view of acid-base metabolism, to a large increase in the intake of acid (hydrochloric acid), an outstanding question for consideration is the possibility that metabolism

of an unusually large amount of this acid may cause an alteration of the base concentrations in the body fluids. The importance of accurately sustained base concentrations within the body has been indicated in the preceding paper.[1] It may be said that the normal structure, in a physicochemical sense, of the body fluids, for example, their osmotic pressure and reaction, is closely dependent on a careful regulation of the extent to which acid substances are permitted to carry fixed alkali into the urine. Even under normal circumstances, fixed alkali must be used in the process of acid excretion with a carefully regulated economy, the total of acid substances claiming excretion in the urine being greatly in excess of the fixed alkali content of usual diets. The administration of hydrochloric acid for a therapeutic purpose provided opportunity for observation of the process of acid excretion under circumstances calling for a very unusual extension of the factors conserving the base content of the body fluids. An understanding of the mechanism accom-

TABLE 2.—*Concentration of Base in Water of Blood Serum and in Water of Muscle Tissue* *

Base	Serum Water, C.c. Tenth Normal per Hundred C.c.	Muscle Water, C.c. Tenth Normal per Hundred C.c.
Sodium	157.7	45.8
Potassium	5.6	108.1
Calcium	5.5	4.9
Magnesium	2.7	23.3
Total	171.5	182.1

* The values for serum water were computed from the average usual amounts of the bases in blood serum by taking the water content of serum as 91 per cent. We are indebted to Kramer and Tisdall for the data used. In obtaining the concentrations given for muscle water Katz' (Footnote 8) measurements of the amounts of the bases in fresh human muscle tissue were used, the water of muscle tissue being taken as 76 per cent.

plishing the regulation of fixed alkali excretion and an appreciation of its very great extensibility are indispensable in a consideration of the effect on the acid-base metabolism of greatly increasing the acid intake. We have, therefore, thought it worth while to describe here in some detail the process of acid excretion and to obtain from the urine following administration of ammonium chlorid and hydrochloric acid such measurements as will serve fairly completely to display in quantitative terms all of the factors in this regulatory function of the kidney.

The character of the base concentrations of the body fluids may first be briefly described. They are composed practically entirely of the sum of the concentrations of sodium, potassium, calcium and magnesium. The base ammonia which binds a large part of the total acid value in the urine is not used to appreciable extent in the body fluids. It is this fact that base concentrations within the body must be composed entirely of fixed alkali which makes necessary a careful regulation of the use of fixed alkali in the process of acid excretion. The base

concentration which is accessible to measurement is that of blood plasma. Estimations of the base in the water of muscle tissue, derived from the data of Katz [8] and given in Table 2, will serve to indicate the probability that the base concentrations in various compartments of body water are of a closely similar size. In this comparison of the base content of an example of extracellular body water with that found in an intracellular portion, it is interesting to note that, although the total base content is roughly the same in both, the concentrations of the individual bases are, except in the case of calcium, widely different; sodium, constituting most of the base in blood serum, and potassium, the greater part in muscle water. The significance of the total concentration (as a controlling factor in the osmotic pressure mechanism) is thus evidently quite apart from the local physiologic purposes of the concentrations of the individual bases.

We are chiefly indebted to L. J. Henderson [9] for our knowledge of the factors which control the extent to which fixed alkali is used in the process of acid excretion. Briefly stated, this regulation depends on the ability of the kidney to secrete a fluid more acid than blood plasma and on a regulated production of ammonia. As regards the locus of this regulated ammonia production, Nash and Benedict [10] have presented good, though perhaps not conclusive, evidence and argument that it takes place in the kidney. Ammonia is, in effect, substituted, as the acid substances enter the urine, for fixed alkali which they bound while being conveyed in the body fluids. The acidity of the urine, on the other hand, represents an absolute saving of base, owing to the fact that certain acid substances bind less base in the urine than they do while being carried in the body fluids. The acid substances which are excreted with less base than they bind while being carried to the kidney are phosphoric acid and organic acids. The base saving in this manner in the elimination of phosphoric acid may be briefly described. Phosphoric acid is present in the body fluids and in urine in the form of both its monobasic and its dibasic salts. In the faintly alkaline blood plasma, much the greater part of the acid is bound as dibasic phosphate (B_2HPO_4). In very acid urine, on the other hand, nearly all of the phosphoric acid is present as monobasic phosphate (BH_2PO_4).[11] The excretion of phosphoric acid in very acid urine is thus accomplished with an expenditure of slightly more than half of the base which it bound while being carried to the kidney. Organic acids, by reason of the fact that they are weakly acid substances, may be present to a slight

8. Katz: Arch. f. d. ges. Physiol. **63**:18, 1896.

9. Henderson, L. J.: Am. J. Physiol. **21**:427, 1908; J. Biol. Chem. **9**:403, 1911; Henderson, L. J., and Palmer, W. W.: J. Biol. Chem. **17**:305, 1914.

10. Nash, T. P., and Benedict, S. R.: J. Biol. Chem. **48**:463 (Oct.) 1921.

11. *B* in these formulas represents an atom of univalent base.

extent unbound at the usual reaction of urine, whereas at the faintly alkaline reaction of blood plasma they must be practically entirely bound. The two remaining urinary acids, hydrochloric and sulphuric, being "strong" acids, i. e., dissociating when in solution practically all of their hydrogen, cannot be present to any appreciable extent in a fluid of such relatively low hydrogen ion concentration as is even very acid urine. These two acids must, therefore, carry their complete equivalence of base into the urine. The acidity of the urine being due chiefly to acid phosphate and slightly, under normal circumstances of metabolism, to free organic acids, the economy of base in the elimination of these substances may, as L. J. Henderson suggested, be easily measured by titrating the urine to the reaction of blood plasma (p_H 7.4), the amount

TABLE 3.—*Indirect Estimation of Fixed Alkali Excretion Illustrating Relationships of the Factors Concerned in the Process of Acid Excretion*

Indirect Measurement of Fixed Alkali Excretion	
Acid excretion in terms of base bound at p_H 7.4:	
Organic acids, directly titrated	= 167 c.c. tenth normal organic acids
Sulphates, 180 mg. sulphur ÷ 3.2 × 2	= 115 c.c. tenth normal H_2SO_4
Phosphates, 381 mg. phosphorus ÷ 3.1 × 1.8	= 223 c.c. tenth normal H_3PO_4
Chlorids, 1,645 mg. chlorin ÷ 3.5	= 470 c.c. tenth normal HCl
	975 c.c. tenth normal total acid excretion
Titratable acidity of urine	= 96 c.c. tenth normal "base economy"
	879 c.c. tenth normal total base excretion
Ammonia, 982 mg. ammonia ÷ 1.7	= 375 c.c. tenth normal NH_3
	504 c.c. tenth normal fixed alkali excretion
Direct Measurement of Fixed Alkali Excretion (Neglecting Magnesium)	
Sodium, 435 mg. ÷ 2.3	= 189 c.c. tenth normal
Potassium, 1,150 mg. ÷ 3.9	= 295 c.c. tenth normal
Calcium, 8 mg. ÷ 4 × 2	= 4 c.c. tenth normal
Total	= 488 c.c. tenth normal

* Data from urine specimen obtained during the first twenty-four hours of hydrochloric acid administration.

of base which must be added to the urine in order to bring it to the faintly alkaline reaction of the plasma being obviously a measure of the base which these substances left behind in the plasma.

We have undertaken to obtain from twenty-four hour urine specimens, collected from this infant during and following the administration of hydrochloric acid and of ammonium chlorid, measurements of the factors controlling fixed alkali excretion and also of the extent to which they have limited the conveyance of fixed alkali into the urine. The latter value was estimated indirectly by subtracting from the total acid excretion (expressed in terms of base bound by the acid substances at the reaction of blood plasma) the sum of the measurements of the titratable acidity of the urine and the ammonia excretion, the value for the total acid excretion being obtained by making separate measure-

ments of the acid substances in the urine; namely, hydrochloric, sulphuric, phosphoric and organic acids. The base bound by phosphoric acid at the reaction of the plasma is taken, on the basis of Sörensen's data, as 1.8 times the molecular concentration of monohydrogen phosphate ($HPO_4^=$).[12] The organic acids are assumed to bind the equivalence of their titration value, as determined by the method of Van Slyke and Palmer. Hydrochloric acid binds one, and sulphuric acid, owing to the divalency of its acid radicle, two equivalents of base. This plan of indirect measurement of fixed alkali excretion by subtracting the titratable acidity of the urine and its ammonia content from the total acid excretion is illustrated in Table 3. Estimation of the fixed alkali excretion in this indirect manner is much easier to accomplish than by direct measurements of the amounts of sodium, potassium, calcium and magnesium in the urine, the methods for determining the bases being more laborious than those by means of which the acid values are obtainable. Our chief purpose, however, in using this plan was to display all of the acid-base factors in the urine and thus to illustrate completely, by means of quantitative data, the process of acid excretion. The value for the fixed alkali excretion obtained in this way cannot be regarded as more than an approximately accurate estimation. That the principles involved are substantially correct and that the result obtained is of an accuracy quite sufficient for illustrative purposes are indicated by the value found for the fixed alkali excretion directly measured in the same specimen (Table 3). This measurement does not contain magnesium and is, therefore, slightly, probably not more than from 2 to 4 c.c. tenth normal, incomplete. It will be seen to agree very satisfactorily with the indirectly determined value.

Data obtained in the manner just described from twenty-four hour specimens of urine collected during and following the administration of ammonium chlorid and of hydrochloric acid are given in Tables 4 and 5. As a basis from which to note the effect of hydrochloric acid ingestion on acid-base values in the urine, a specimen obtained several days before giving hydrochloric acid was also analyzed. A specimen was, for the same purpose, collected the day before administration of ammonium chlorid. The data from this specimen are not given, as it was found that they were for the most part much smaller values than were obtained from the specimen collected before the hydrochloric acid period. This is believed to have been due to an unusual retention of food substances in consequence of the fact that this was the first day

12. According to Sörensen's measurements, in a solution of p_H 7.4 and containing salts of phosphoric acid, 20 per cent. of the monohydrogen phosphate (HPO_4) is bound as BH_2PO_4 and 80 per cent. as B_2HPO_4. The base (B) bound by phosphoric acid at p_H 7.4 is, therefore, $0.2 + (0.8 \times 2) = 1.8$ times the molecular concentration of the monohydrogen phosphate ion.

TABLE 4.—*Acid and Base Excretion Following Ingestion of Ammonium Chlorid*

Day of Experiment	Volume C.c.	p_H	Acid Excretion in Terms of Base Bound in Plasma					Base Economy (Titr. Acid) C.c. Tenth Normal	Total Base Excretion, C.c. Tenth Normal	Ammonia Excretion, C.c. Tenth Normal	Fixed Base Excretion, C.c. Tenth Normal	Creatinin, C.c. Tenth Normal
			Organic Acids, C.c. Tenth Normal	H_2SO_4 C.c. Tenth Normal	H_3PO_4 C.c. Tenth Normal	HCl C.c. Tenth Normal	Total Acid Excretion, C.c. Tenth Normal					
1. 750 c.c. tenth normal NH_4Cl	410	6.2	131	103	198	278	**710**	88	622	301	**321**	115
2. 750 c.c. tenth normal NH_4Cl	790	5.8	153	114	261	945	**1,473**	149	1,324	577	**747**	118
3. 750 c.c. tenth normal NH_4Cl	550	5.8	156	123	189	822	**1,290**	112	1,178	786	**392**	108
4. No NH_4Cl	760	6.5	146	90	147	491	**874**	46	828	576	**252**	105
5. No NH_4Cl	750	6.5	148	116	170	230	**664**	54	610	224	**386**	102

TABLE 5.—*Acid and Base Excretion Following Hydrochloric Acid Ingestion*

Day of Experiment	Volume C.c.	p_H	Acid Excretion in Terms of Base Bound in Plasma					Base Economy (Titr. Acid) C.c. Tenth Normal	Total Base Excretion, C.c. Tenth Normal	Ammonia Excretion, C.c. Tenth Normal	Fixed Base Excretion, C.c. Tenth Normal	Creatinin, C.c. Tenth Normal
			Organic Acids, C.c. Tenth Normal	H_2SO_4 C.c. Tenth Normal	H_3PO_4 C.c. Tenth Normal	HCl C.c. Tenth Normal	Total Acid Excretion, C.c. Tenth Normal					
1. No HCl	440	6.8	145	100	192	233	**670**	33	637	230	**407**	106
2. 750 c.c. tenth normal HCl	650	6.2	167	115	223	470	**975**	96	879	375	**504**	130
3. 750 c.c. tenth normal HCl	790	5.9	171	115	279	1,000	**1,565**	145	1,420	688	**732**	126
4. No HCl	530	6.4	158	96	194	510	**958**	72	886	568	**318**	121
5. No HCl	560	6.8	149	91	174	312	**726**	31	695	380	**315**	115
6. No HCl	450	6.7	125	99	166	228	**618**	34	584	198	**386**	107

of the period during which a liter of whole milk was given, following a very inadequate food intake. The data from the specimen collected the second day following cessation of ammonium chlorid administration are approximately of the same values as those from the foreday of the hydrochloric acid period, and may, therefore, be regarded as better serving the purpose of basal data with which to compare the alteration in values caused by ammonium chlorid ingestion. The data from the ammonium chlorid period cannot, however, be regarded as so satisfactory as those representing the effect of hydrochloric acid ingestion, because of this lack of a sufficiently long fore period on the diet used and the consequent uncertainty of stationary retention values, aside from

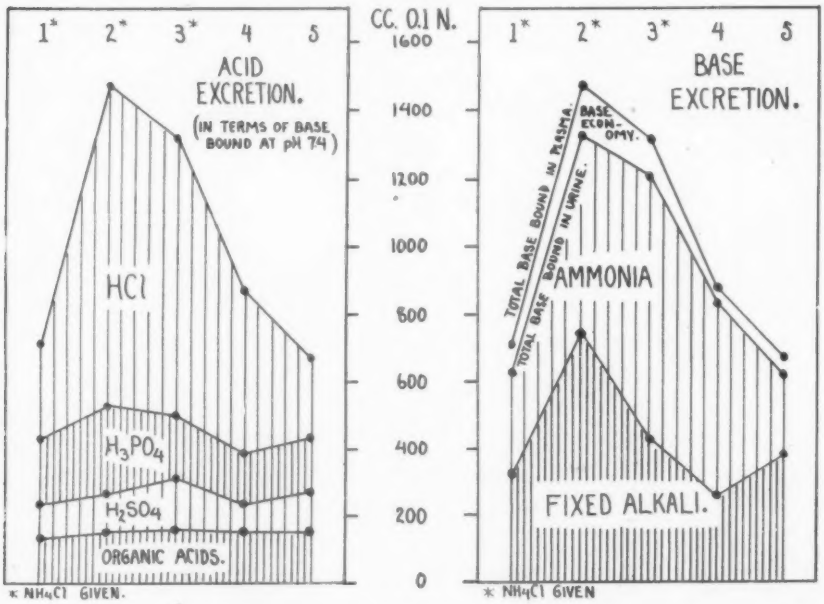

Fig. 1.—Acid and base excretion following ingestion of ammonium chlorid; diagrams constructed from data in Table 4.

the effect on these values of the ingested ammonium chlorid. Moreover, the collections in two instances (the first and the fourth day specimens) were incomplete during this period. This fault was roughly repaired by estimating the twenty-four hour values in these specimens on a basis of interpolated values for creatinin excretion. So far as the data are used to show the manner of acid-base excretion, it is believed that this illustrative purpose is not seriously interfered with by the lack of absolute accuracy in the values given. The values given in Tables 4 and 5 are arranged according to the plan indicated in Table 3. The data given in the tables are reproduced graphically in Figures 1 and 2. In these charts the diagram on the left

represents the acid excretion. The values for the individual acids being superimposed, the top line measures, from the base line, the total acid excretion. The manner in which base is used in the elimination of this total acid excretion is indicated by the diagram on the right. The top line in this diagram is transferred from the diagram on the left; i. e., it measures from the base line the base bound by the total acid excretion while being carried for excretion. Laying off downward from the points on this line the measurements of the titratable acidity of the urine, "base economy" is indicated and a line obtained which measures from the base line the total of base carried into the urine. Laying off again the measurements of ammonia in the urine, the remainder of the

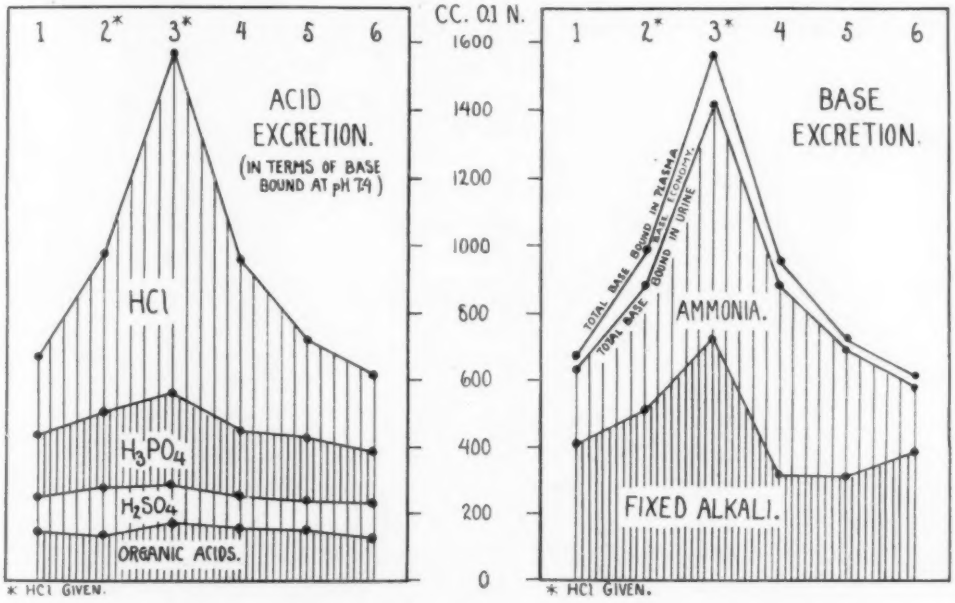

Fig. 2.—Acid and base excretion following ingestion of hydrochloric acid; diagrams constructed from data in Table 5.

distance to the base line measures the fixed alkali excretion. These diagrams, it is believed, will serve to illustrate rather more clearly than the data in Tables 4 and 5 the operation of the factors which control the extent to which fixed alkali is used in the process of acid excretion. The large need for regulation of fixed alkali excretion is indicated by the fact that the total acid excretion was doubled by the amounts of ammonium chlorid and of hydrochloric acid given. The much greater size of the ammonia factor is apparent. The "base economy" factor is not, except under circumstances producing large increase in the excretion of phosphoric acid or of organic acids, widely extensible. We have noted, however, from other data, that on usual diets its value,

as might be expected, is considerably more variable from day to day than the ammonia excretion, and we venture the conjecture that this factor may be regarded as the "fine adjustment" of the mechanism regulating fixed alkali excretion.

The data from the ammonium chlorid period of the experiment serves, as well as those obtained following hydrochloric acid administration, the purpose of illustrating the operation of the factors controlling fixed alkali excretion. Presumably, regardless of the extent to which ammonia is ingested, it will enter the urine to an extent regulated

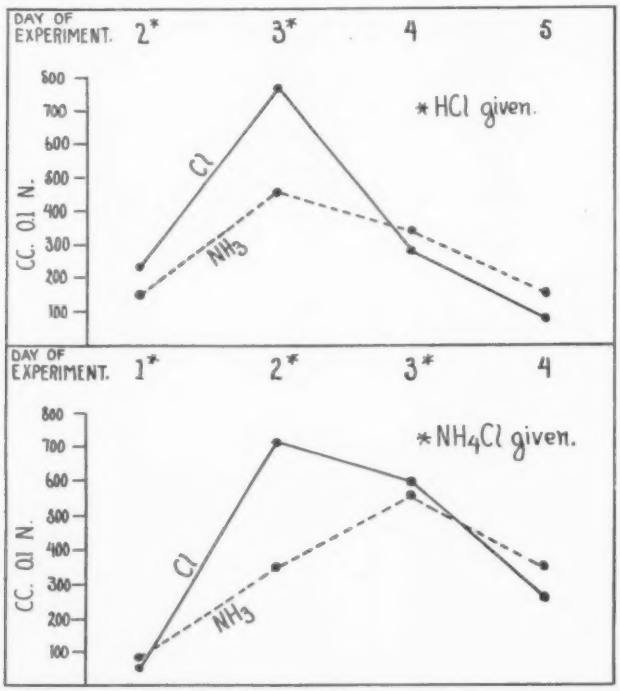

Fig. 3.—Increase in excretion of chlorin and of ammonia in urine during hydrochloric acid and ammonium chlorid periods.

according to the need for conservation of fixed alkali. The regulated use of ammonia following ingestion of ammonium chlorid is quite apparent when the amounts of ammonia and of chlorin estimated, as derived from the ingested ammonium chlorid, are compared. To present this comparison the diagrams in Figure 3 were constructed. The values there charted represent the increase in the urine of ammonia and of chlorin following the ingestion of ammonium chlorid. They were obtained by subtracting from the total values for the days indicated the values found in the urine collected during the second day following cessation of ammonium chlorid administration. Inspection of the

diagram will make clearly evident the fact that the excretion of ammonia and of chlorin from ingested ammonium chlorid are separately controlled. Chlorin is seen to enter the urine more rapidly than ammonia. The figure also contains a diagram representing the increase in chlorin and ammonia in the urine following the administration of hydrochloric acid. The curves obtained are of quite the same character as those of the ammonium chlorid period, and the inference is that, at least from the point of view of the process of acid excretion, the ingested ammonium chlorid may be regarded as hydrochloric acid. More precise evidence in support of this surmise may be obtained by noting the ratio of ammonia to chlorin in the urine in both periods, using total values for the two days of hydrochloric acid administration and for the first two days of the three day ammonium chlorid period. The data obtained from Tables 4 and 5 are these:

Ammonium chlorid period: ammonia, 878 c.c. tenth normal; chlorid (Cl^-), 1,223 c.c. tenth normal; $\frac{NH_3}{Cl} = 0.72$.

Hydrochloric acid period: ammonia, 1,063 c.c. tenth normal; chlorid (Cl^-), 1,470 c.c. tenth normal; $\frac{NH_3}{Cl} = 0.72$.

The absolute agreement of the ammonia to chlorid ($\frac{NH_3}{Cl}$) ratio is striking and would seem to permit with certainty the inference that the effect of administering ammonium chlorid is, from the point of view of acid excretion, the same as would be obtained from placing its equivalence as hydrochloric acid in the milk.

3. THE MANNER OF THE EFFECT OF AN INCREASED METABOLISM OF HYDROCHLORIC ACID ON THE EXCRETION IN THE URINE OF OTHER ACID SUBSTANCES AND OF FIXED ALKALI

The manner of the control of fixed alkali excretion is fairly completely indicated by the data in Tables 4 and 5 and by means of Figures 1 and 2. It is evident, however, from these tables and figures that following the ingestion of ammonium chlorid and of hydrochloric acid there occurs a large increase in the excretion of fixed alkali. Since the data from the hydrochloric acid period of the experiment (Table 5) are more complete and of a better degree of accuracy than those representing the effect of ammonium chlorid ingestion, they will be used as a basis for consideration of the probable significance of the increased excretion of fixed alkali. An estimation of the size of the increase in fixed alkali excretion may be arrived at by comparing the amount of fixed alkali eliminated when hydrochloric acid was given with the amount found in the urine collected during the foreday. Thus, the fixed alkali excretion during the two days of hydrochloric acid administration was (Table 5) 504 plus 732 = 1,236 c.c. tenth normal. For the foreday this value was 407 c.c. tenth normal. Regarding this as a stationary value for the diet used, the excretion for two days should be

814 c.c. tenth normal, and the increase when hydrochloric acid was given may be taken as 1,236—814 = 422 c.c. tenth normal, approximately a 50 per cent. increase. It may also be deduced from the data in Table 5 that immediately following cessation of hydrochloric acid ingestion, the inorganic base excretion fell below its foreday value to the extent of 89 plus 92 plus 21 = 202 c.c. tenth normal, for the three days that it was measured, indicating a recovery during this period of about one half of the base lost during hydrochloric acid administration.

It may also be seen in Table 5 and in Figure 2 that when hydrochloric acid is given there occurs an increase in the excretion of the other three urinary acids. During the foreday the excretion of organic acids plus sulphuric acid plus phosphoric acid amounted to 437 c.c. tenth normal. For each of the two days when hydrochloric acid was given, the sum of these acids was 505 and 565 c.c. tenth normal, respectively. The increase in excretion of acids other than hydrochloric acid may, therefore, be taken as 68 plus 128 = 196 c.c. tenth normal. Of this increase it may be estimated, from the data in Table 5, that 128 c.c. tenth normal is due to increase in the excretion of phosphoric acid.

There is thus presented for consideration the fact that an increase in the metabolism of hydrochloric acid has caused an increase in the excretion of fixed alkali and also an increase in the excretion of urinary acids (other than hydrochloric acid), especially of phosphoric acid. In explanation of this fact in general terms, a choice between two hypotheses is indicated.

1. An increase in metabolism of hydrochloric acid brings about a withdrawal of fixed alkali from the body fluids, presumably in consequence of the unusual size of the acid excretion, and also in a manner quite obscure causes withdrawal from the body fluids of other acid substances. If this is the case the effect of hydrochloric acid administration is to reduce base concentrations within the body and also concentrations of acid substances, especially that of phosphoric acid (as phosphates).

2. The alternative explanation assumes that the unusual size of the chlorid excretion has produced a withdrawal of body water. In proportion to the reduction of the volume of body fluids an increased amount of base will obviously become available for use in the process of acid excretion without reduction of base concentrations. As regards the possibility of a reduction of the volume of body fluids causing an increase in the excretion of acid substances may be noted the huge concentration of chlorid (Cl^-) in the blood plasma and (according to the data of Katz [8]) a probably considerable concentration of phosphates in the water of muscle tissue.

From these two hypotheses widely different inferences as regards the effect of hydrochloric acid ingestion on acid-base values in the body fluids are to be obtained. Base concentrations, for instance, are either considered to be reduced in consequence of an excessive base excretion or are believed to be correctly sustained, the extra fixed alkali in the urine being explained as derived from lost body water. It is, indeed, quite impossible to proceed in a consideration of the effects of hydrochloric acid ingestion without first coming to a decision as to the probable cause of the increased excretion of fixed alkali and of acid substances. We wish to present here an interpretation of the data at hand favoring the view that the extra fixed alkali in the urine and the increased excretion of acid substances are caused by a loss of body fluids. Assuming a reduction in the volume of body fluids, we will expect an increase in chlorid (Cl^-) excretion apart from the increase due directly to chlorid (Cl^-) added to the intake. The chlorid (Cl^-) contained in the lost body water may, without affecting base concentrations, carry into the urine the fixed alkali which it bound in the body fluids. This portion of the chlorid (Cl^-) excretion should, therefore, exert no demand for extension of the base saving factors (titratable acidity and ammonia). It may, therefore, be undertaken to measure the part of the chlorid (Cl^-) excretion due to loss of body water by comparing the extension of the base saving factors with the increase in chlorid (Cl^-) elimination. For the two days of hydrochloric acid administration the increase in titratable acidity plus ammonia is found from the data in Table 5 to be 778 c.c. tenth normal. The increase in hydrochloric acid excretion for these two days is 1,004 c.c. tenth normal. It is thus seen that 226 c.c. tenth normal of the increase in hydrochloric acid excretion is not covered by extension of the base saving factors and may, on the basis of an assumption of a loss of body water, be explained as chlorid (Cl^-) entering the urine along with the fixed alkali which carried it within the body. Justification for applying the extension of the base saving factors entirely to the excretion of the ingested hydrochloric acid is contained in the conception that the increased excretion of the other acid substances, being also a consequence of a loss of body water, permits their carrying with them the inorganic base which they bound in the body fluids. It was noted above that the estimated increase in the fixed alkali excretion during the two days of hydrochloric acid administration was 422 c.c. tenth normal and that the increase in the urinary acids other than hydrochloric acid was 196 c.c. tenth normal. Assuming that the increase in fixed alkali excretion was a consequence of a reduction of the volume of body fluids, we obtain again $422-196=226$ c.c. tenth normal as the portion of the increased chlorid (Cl^-) excretion due to the same cause. Regarding the loss of body water as due to a large increase in the metabolism of

hydrochloric acid, the fact that chlorid (Cl^-) is carried chiefly in extracellular body water, blood plasma, for example, suggests that the loss of water will occur chiefly at the expense of extracellular fluids. In blood plasma 66 per cent. of the inorganic base is bound by chlorid (Cl^-). In approximate agreement with this value the 226 c.c. tenth normal chlorid (Cl^-) assumed to be derived from lost body water is 54 per cent. of the equivalence of the increase in inorganic base excretion (422 c.c. tenth normal), which is being regarded as from the same source. In further defense of the conception of a reduction of the volume of body water as a reasonable means of explaining the facts at hand, it may be noted that, in contrast to the alternative view, it accounts for the increase in the excretion of acids as well as of base, and it credits the kidney with being able to maintain a correct control of acid-base excretion. To our minds, it is much more in accord with the known principles of acid-base excretion.

The assumption of a loss of body water is supported by the fact that a large increase in the volume of urine occurred when hydrochloric acid was given (Table 5), the urine volume for the foreday being 440 c.c.

TABLE 6.—*Concentration of Sodium in Blood Serum After Administration of Ammonium Chlorid, Calcium Chlorid and Hydrochloric Acid*

	Na Mg. per 100 C.c.
NH_4Cl given for two days	333
Two days after discontinuing NH_4Cl	326
$CaCl_2$ given for two days	320
HCl given for two days	327

and for each of the two days of hydrochloric acid administration, 650 and 790 c.c., respectively.[13] Regrettably the infant was not weighed directly before and following the hydrochloric acid period. A large loss of body weight during the three days of ammonium chlorid administration, 540 gm., was, however, measured and constitutes emphatic evidence of a loss of body water.

The concentration of base in the blood serum of this subject was not completely measured, although a few determinations of sodium were made. Since sodium constitutes 92 per cent. of the base in blood serum, the size of the total base concentration may be assumed to be fairly closely indicated by a measurement of sodium alone. The values found are given in Table 6, and it may be seen that they approximate

13. Throughout the entire period of whole milk feeding the stools were formed and unusually dry. There was, therefore, no appreciable variation of water loss by way of the bowel. The stools were collected the day before and the first day following hydrochloric acid administration and their chlorin content was determined. The very small amounts found, 13 c.c. tenth normal and 6 c.c. tenth normal for each twenty-four hours, respectively, are negligible in relation to the measurements of hydrochloric acid metabolism obtained from the urine.

very closely the average usual value, 330 mg. per hundred cubic centimeters of serum. The fact that the concentration of this chief base in the blood serum was not found to be measurably reduced in the presence of the large increase in the excretion of fixed alkali occurring during the first two days of ammonium chlorid and of hydrochloric acid administration makes the inference permissible that the regulation of inorganic base excretion was closely correct. In the preceding paper, we [1] noted that the total base concentration, measured by determining separately the amounts of sodium, potassium, calcium and magnesium present, was not appreciably altered by the administration of calcium chlorid, although there occurred just preceding the measurements of base in the serum a large increase in the excretion of fixed alkali in the urine.

It is, we believe, the evidence of these data that the increased excretion of acids and fixed alkali in the urine following an increase in the metabolism of hydrochloric acid may best be explained as at least chiefly a consequence of a loss of body water and probably not, to an appreciable extent, derived at the expense of concentrations in the body fluids. These data are not, however, of a precision to prove that a slight loss from concentrations within the body does not occur.

Scheer [5] noted the increased phosphoric acid elimination in the urine following administration of "hydrochloric acid milk." By means of measurements of phosphorus in the stools, he was able to show that the increase in the urine was largely a consequence of an increased absorption. Hydrochloric acid may as Scheer points out, very reasonably be assumed to promote absorption of phosphates. Such an effect would not, however, be expected from ingestion of ammonium chlorid. György [14] has demonstrated quite thoroughly that an increase in phosphate elimination follows ammonium chlorid administration. He has inferred from this fact a lag in the intermediary metabolism of phosphoric acid in tetany which is in some way corrected by the large increase in acid metabolism following the ingestion of ammonium chlorid. We do not wish to deny that this may be the case. We prefer, however, the less elaborate and, to our minds, much more probable conception that the increased phosphate excretion is due simply to a reduction of the volume of the body fluids caused by the diuretic action of ammonium chlorid.

4. THE MANNER OF THE EFFECT OF AN INCREASED METABOLISM OF HYDROCHLORIC ACID ON THE PLASMA BICARBONATE

The fact that the bicarbonate of the blood plasma may be lowered by the ingestion of ammonium chlorid was demonstrated by Haldane.[4] Scheer [5] measured a considerable reduction of the bicarbonate of the

14. György, P.: Jahrb. f. Kinderh. **99**:104 (Aug.) 1922.

plasma of infants with tetany while receiving "hydrochloric acid milk." With F. F. Tisdall,[1] we found a decrease in the plasma bicarbonate following the administration of calcium chlorid to infants and were, moreover, able to demonstrate that the lowering of bicarbonate was due in large part, perhaps entirely, to increase in the chlorid concentration. The total base concentration in the serum was not found to be measurably reduced. The reduction of bicarbonate could not, therefore, be due, to an appreciable extent, to a withdrawal of base from the plasma. We have given above evidence indicating that, although a large increase in fixed alkali excretion occurs following the administration of ammonium chlorid or of hydrochloric acid (as was also found to occur following the ingestion of calcium chlorid), the total concentration of base in blood serum is not appreciably diminished, presumably because of a loss of water corresponding to the increased excretion of

TABLE 7.—*Concentration of Bicarbonate and of Chlorids in Blood Serum Before and Following Administration of Ammonium Chlorid, Calcium Chlorid and of Hydrochloric Acid*

Date		$BHCO_3$		BCl		$BHCO_3$ + BCl
		Per Cent. by Volume of Carbon Dioxid	C.c. Tenth Normal per 100 C.c.	Gm. NaCl per 1,000 C.c.	C.c. Tenth Normal per 100 C.c.	C.c. Tenth Normal per 100 C.c.
May 6	Before giving NH_4Cl	57.0	25	6.07	105	130
8	NH_4Cl given for 2 days	29.6	13	7.00	121	134
9	NH_4Cl given for 3 days	37.2	17	6.67	115	132
11	NH_4Cl discontinued for 2 days	57.9	26	6.00	104	130
May 13	$CaCl_2$ given for 2 days	31.9	14	6.67	115	129
16	$CaCl_2$ discontinued for 2 days	54.1	24	5.98	102	126
June 5	Before giving HCl	52.3	23	6.07	105	128
7	HCl given for 2 days	31.9	14	6.87	119	133
10	HCl discontinued for 3 days	44.9	20	6.13	106	126

fixed alkali. Coinciding with this view, the measurements of bicarbonate and of chlorid in the serum given in Table 7 show an approximately equivalent inverse alteration following the administration of ammonium chlorid or of hydrochloric acid which precludes the necessity of assuming a decrease in base in explanation of the lowering of bicarbonate. The table also includes measurements representing the effect of calcium chlorid ingestion. The amounts of bicarbonate and of chlorid found are expressed in the usual terms, percentage by volume of bound carbon dioxid and grams of sodium chlorid per liter, respectively, and also, in order to compare the extent of their alterations in equivalent terms, as cubic centimeters of tenth normal base bound per hundred cubic centimeters of serum. A large decrease in bicarbonate accompanied by an increase in chlorids may be seen following the administration of ammonium chlorid, calcium chlorid or hydrochloric acid. The approximately stationary value for the sum of the concentrations of chlorid (Cl^-) and bicarbonate (HCO_3^-) in terms of base bound given in the

last column of the table brings out clearly their closely inverse relationship and is also evidence that the usual amount of base in the serum for the binding of chlorid (Cl^-) plus bicarbonate (HCO_3^-) has not been appreciably altered. Further illustration of this point is provided by the diagram in Figure 4. The concentrations of chlorid (Cl^-) and of bicarbonate (HCO_3^-) in terms of base bound per hundred cubic centimeters of serum are here superimposed. The lower of the dotted lines across the chart represents the usual average concentration of BCl, and the upper dotted line, the amount of base bound by the sum of the average concentrations of chlorid (Cl^-) and bicarbonate (HCO_3^-), the intervening space thus representing the usual concentration of BHCO$_3$. It will be seen that the amount of base bound by

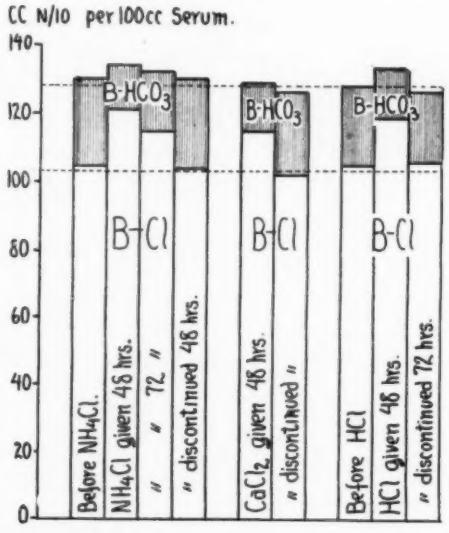

Fig. 4.—Close relationship of the bicarbonate lowering and chlorid increase following administration of ammonium chlorid, calcium chlorid and hydrochloric acid. The measurements obtained, given as cubic centimeters tenth normal per hundred cubic centimeters of serum, are superimposed in the diagrams.

chlorid (Cl^-) plus bicarbonate (HCO_3^-) remains a nearly stationary value, so that with increase in BCl there occurs, necessarily, reduction of BHCO$_3$. With disappearance of the excessive BCl concentration, BHCO$_3$ resumes its usual size. The diagram makes quite clear the fact that the decrease in bicarbonate following ingestion of ammonium chlorid, calcium chlorid or hydrochloric acid is, for the most part, perhaps entirely, to be explained by an increase in chlorid at the expense of bicarbonate and is not to an appreciable extent caused by reduction of the absolute amount of base in the serum. There is, indeed, in the diagram a suggestion of a slight increase in the amount of base bound

by chlorid (Cl^-) plus bicarbonate (HCO_3^-). As the appreciable rise in this value may be seen following ingestion of each of the substances used, it is probably not a product of error in the two measurements. It may be explained by assuming a slight shift of reaction in the direction of acidity. This would cause a small reduction in the amount of base bound by phosphoric acid and protein with equivalent increase in base available for binding carbonic acid.

An interesting significance of these data is the apparently specific manner of the reduction of bicarbonate following the ingestion of hydrochloric acid or of hydrochloric acid producing substances. The lowered bicarbonate is probably not simply a consequence of ingestion of an unusual amount of unoxidizable acid. It is doubtless closely related to the fact that chlorin, as compared with other acid ions in the plasma, is held at a huge concentration, covering, when of usual average size, three fifths of the base in the plasma. An unusual demand for the transport of chlorin entering the body fluids without an equivalent of base may be expected to increase the chlorin concentration to an extent which, though not large in relation to the usual concentration, will greatly alter the amount of base available for binding carbonic acid.

5. THE REACTION OF THE BLOOD PLASMA IN THE PRESENCE OF AN INCREASED METABOLISM OF HYDROCHLORIC ACID

Demonstration of a reduction of bicarbonate in the plasma does not constitute evidence of a shift of its reaction in the direction of acidity. The reaction of the plasma may be said to be chiefly determined by the ratio of free to bound carbonic acid. The concentration of free carbonic acid in the plasma is determined by the tension of carbon dioxid in the alveolar air spaces, and the latter value is under control of the respiratory mechanism. A large reduction of the carbon dioxid tension in the alveolar air spaces may, for instance, be brought about by the simple maneuver of greatly increasing the volume of lung ventilation (hyperpnea). With reduction of the carbon dioxid tension in the alveolar air, the concentration of free carbonic acid in the plasma will fall correspondingly. The respiratory mechanism is thus potentially able to compensate over a wide range for a reduced bicarbonate by effecting a decrease in the free carbonic acid of the plasma of such extent that the usual $H_2CO_4 : BHCO_3$ ratio (1 : 20) will be maintained and a change in reaction of the plasma avoided.

It is usually assumed that all except excessive reductions of the plasma bicarbonate from any cause are compensated for, through the agency of the respiratory center, to such an extent as to prevent an appreciable alteration in the reaction of the plasma. Such a generalization is probably incorrect. Regarding the blood as a physicochemical mechanism, the quite absolute interdependence of its structural parts

has been illustrated and emphasized by L. J. Henderson.[15] It is, therefore, probably not permissable to postulate a stationary reaction of the plasma on the basis of a potential ability of the respiratory center to provide it. It is, for instance, conceivable that certain alterations in the structure of this mechanism would make necessary its operation at a p_H differing from the usual one.

It was, therefore, desirable to measure directly the p_H of the serum in the presence of a lowered bicarbonate brought about in a particular manner by the increase in hydrochloric acid metabolism. For this purpose the recently devised colorimetric method of Cullen was used. Unfortunately we became equipped for this method only before the last (hydrochloric acid) period of the experiment. The measurements of p_H of the blood serum obtained during this period were as follows: before giving hydrochloric acid, 7.39; after giving hydrochloric acid for two days, 7.22, and after hydrochloric acid was discontinued for three days, 7.34. Their significance should be considered with the circumspection required by the fact that they constitute a single set of observations. It must also be said regarding them that the standards used, although carefully prepared according to Cullen's specifications, were not electrometrically tested. The measurements cannot, therefore, be warranted as regards their absolute values. They may, however, be taken as dependably demonstrating and approximately measuring a change of reaction in the direction of acidity in the blood serum of this subject following ingestion of hydrochloric acid. We do not wish to offer conjecture as to the cause of so considerable a change of reaction following a reduction of bicarbonate of a degree presumably well within the range of compensation by respiratory adjustment.

It may be noted that demonstration of an actual change of reaction supports the explanation of the small contribution to the base available for binding bicarbonate noted in the preceding section.

The outcome of these p_H measurements in the serum following hydrochloric acid ingestion indicates the possibility that an increase in hydrogen ion concentration may also be a factor in the therapeutic action of these hydrochloric acid producing substances.

6. THE PROBABLE THERAPEUTIC SIGNIFICANCE IN TETANY OF REDUCTION OF BICARBONATE AND INCREASE IN HYDROGEN ION CONCENTRATION IN THE BLOOD SERUM

Physiologists have shown that each of the bases found in the body fluids exerts an effect on neuromuscular excitability, that of sodium and potassium being augmentative in contrast to a depressant action by calcium and by magnesium. It is probable that the normal degree of excitability of the neuromuscular mechanisms is the result of a correct

15. Henderson, L. J.: J. Biol. Chem. **46**:411 (April) 1921.

balance in these antagonistic effects and is maintained by reason of closely stationary values for the separate concentrations of the four bases in the body fluids. Howland and Marriott [2] have demonstrated that the calcium concentration is a strikingly constant value in blood serum of infants, except in the case of infants manifesting symptoms of active tetany. The serum from infants with tetany is found to contain greatly less, often only half as much, calcium as the serum of normal infants or infants suffering from other ailments than tetany. The data derived from Katz' analyses given in Table 2 indicate approximately the same concentration of calcium in the water of muscle tissue as in the water of blood serum and permit the surmise that the intracellular and extracellular concentrations of calcium will vary together. Evidence of appreciable alterations in infantile tetany of the usual concentrations of the other three bases, at least in blood serum, has not been found. For instance, the few measurements of sodium, the chief base in the serum, given above, are close to the average value. Owing to the deficiency of calcium in tetany, demonstrable in the blood serum and probably extending throughout the body fluids, the normal balance of the antagonistic effects of the bases may be assumed to be altered in a direction lowering the threshold of neuromuscular excitation.

The low calcium content of the serum found in infantile tetany would thus seem clearly to be indicated as the cause of the increased neuromuscular irritability. We wish now to consider the probable manner of a therapeutic effect from lowering of the bicarbonate or increase of the hydrogen ion concentration of the serum. As indication of a relationship of the size of the bicarbonate concentration and of the degree of acidity of the plasma to the state of excitability of the neuromuscular mechanism, it may be cited that in gastric tetany the bicarbonate concentration is greatly increased,[16] and, in the experimental tetany produced by overbreathing, the reaction of the plasma shifts in the direction of alkalinity,[17] and that in both of these types of tetany the calcium concentration of the serum is not diminished. We are indebted to Freudenberg and György [18] for pointing out the usefulness of the results of a study by Rona and Takahaski [19] of the factors determining the solubility of calcium carbonate in blood serum as a means of explaining the manner in which the bicarbonate concentration and the reaction of the serum may be concerned in the presence or in the disappearance

16. McCann, W. S.: J. Biol. Chem. **35**:553 (Sept.) 1918; McCallum, W. G., Lintz, J., Vermilye, H. N., Leggett, T. H., and Boas, E.: Bull. Johns Hopkins Hosp. **31**:1 (Jan.) 1920; Hastings, H. B., Murray, C. D., and Murray, H. A.: J. Biol. Chem. **46**:223 (March) 1921.

17. Collip, J. B., and Backus, P. L.: Am. J. Physiol. **51**:568 (April) 1920; Grant, S. B., and Goldman, A.: Am. J. Physiol. **52**:209 (June) 1920.

18. Freudenberg, E., and György, P.: Jahrb. f. Kinderh. **96**:5, 1921.

19. Rona, P., and Takahaski, D.: Biochem. Zitschr. **49**:370, 1913.

of the symptoms of tetany. The significance of the degree of solubility of calcium carbonate in blood serum is that only that part of the total calcium present in serum which is in true solution (as calcium carbonate) can be regarded as capable of providing ionized calcium. Presumably, calcium exerts its physiologic effect only to such extent as physicochemical conditions permit its presence as ionized calcium. Rona and Takahaski derived on theoretical grounds the following simple equation to express the dependence of the degree of ionization of calcium in blood serum on the size of the concentrations of bicarbonate and of hydrogen ions: $\frac{(Ca^{++})\ (HCO_3^-)}{(H^+)} = \text{Constant}$, and were able to establish it by direct measurements of the solubility of calcium carbonate (determined by measuring calcium) in solutions containing various amounts of bicarbonate and of differing degrees of reaction. The formula when applied to these measurements was found to give a closely constant value. If the significance of these results is correctly transferable to blood plasma, the extent to which ionized calcium may be present in the plasma may be taken to be determined by the size of the bicarbonate and of the hydrogen ion concentrations. According to the formula, increase in bicarbonate will diminish ionized calcium, whereas increase in hydrogen ion concentration will permit a larger concentration of ionized calcium.

By means of the following modification by Michaelis [20] of Rona and Takahaski's formula the amount of ionized calcium which should be present in blood plasma at given bicarbonate and hydrogen-ion concentrations may easily be calculated;

$$(Ca) = 340 \times \frac{(H)}{(HCO_3)} \text{ mol per liter}$$

Taking the normal p_H of the plasma (of venous blood) as 7.25 [21] and the bicarbonate as 55 per cent. by volume, and using the molar equivalents of these values [22] in the formula, the calculated amount of ionized calcium is approximately 3 mg. of calcium per hundred cubic centimeters; i. e., about one third of the total calcium normally present. In tetany the reduction of total calcium is rarely below 5 mg. per hundred cubic centimeters of plasma, and there is, therefore, present

20. Michaelis, L.: Die Wasserstoffionen-Konzentration, Berlin, **1**:71, 1922.

21. It will be noted that the average usual reaction of the plasma is here taken as p_H 7.25, whereas in the preceding section dealing with the process of acid excretion a plasma p_H of 7.4 was assumed. This discrepancy is regretted. The older value, p_H 7.4, was used in titrating the urines as a result of habit. Recent evidence has indicated that the normal reaction of the plasma is probably more accurately taken as p_H 7.25. The measurements of "base economy" in the excretion of acid in the urine given in the preceding section, may, therefore, be regarded as a trifle larger than they should be.

22. The concentration of bicarbonate (HCO_3^-) should, according to Michaelis, be multiplied by 0.9 to allow for undissociated $BHCO_3$.

enough calcium to provide 3 mg. of ionized calcium (Ca^{++}), assuming hydrogen ion (H^{+}) and bicarbonate ion in (HCO_3^{-}) concentrations are of usual size and that there is no interference with the operation of these factors in determining the concentration of calcium ions (Ca^{++}) in the manner indicated by the foregoing formula. Evidently, however, the reduction of total calcium does in some way interfere with the ionization of calcium to a usual extent. Conceivably, however, the lowered calcium ion concentration in tetany may be raised to its usual value, without increasing the total calcium by sufficiently altering the two factors, hydrogen ion and bicarbonate ion concentrations, in a manner favoring the ionization of calcium. A marked lowering of the plasma bicarbonate has been demonstrated above, following the administration of hydrochloric acid producing substances, and following the ingestion of hydrochloric acid, a very considerable increase in hydrogen ion concentration. These alterations of bicarbonate ion and hydrogen ion concentrations are in the direction which, according to Rona and Takahaski's formula, should increase the ionization of calcium, and it may, therefore, very reasonably be concluded that these changes are directly effective in causing the disappearance of the symptoms of tetany.

The manner in which a reduction of total calcium causes a lowering of ionized calcium is not clear. In order to discuss this point the forms in which calcium is carried in the plasma may be briefly described. As has been mentioned, the concentration of ionized calcium calculated by means of Rona and Takahaski's formula is approximately one third of the usual total calcium content. This theoretical value has recently been confirmed by direct measurements of the ionized calcium in the plasma, made by Brinkman and Van Dam.[23] It is the evidence of dialysis experiments that approximately another one third of the usual total calcium is bound by protein.[19] The character of the remaining one third of the plasma calcium has not been satisfactorily explained. Rona and Takahaski [19] have conjectured that this fraction of the total calcium is held as calcium carbonate in excess of the limits of a true solution of this salt as determined by the physicochemical factors in the plasma. The calcium thus held as calcium carbonate in supersaturated solution is assumed to be nondissociable. If this admittedly somewhat difficult conception is correct, the surmise is permissible that a reduction of total calcium in the plasma would be at the expense of calcium held in supersaturated solution, and should not, unless very extensive, cause a lowering of the concentration of ionized calcium. Another point which should be considered here is the possibility that the decrease of ionized calcium in tetany may, at least in part, be due to a reduction of

23. Brinkman, R., and Van Dam, E.: Kon. Akademie van Wetenschappen te Amsterdam, Proceedings **22**:762, 1920.

hydrogen ion concentration. The concentration of bicarbonate in the tetany of infants has been observed to be of a usual degree. We are not, however, satisfactorily informed as to the values which obtain for hydrogen ion concentration in untreated tetany. It is conceivable that the lowering of ionized calcium is largely a consequence of an abnormally low hydrogen ion concentration. It may be pointed out, however, that a very large decrease in hydrogen ion concentration would be necessary to cause a considerable reduction of ionized calcium. For instance, bicarbonate remaining at its usual value (55 per cent. by volume), it may be calculated by means of the foregoing formula that the p_H of the plasma would have to become 7.55 (probably near or past the physiologic limit of alkalinity) in order to depress the ionization of calcium below 2 mg. per hundred cubic centimeters. A measurement of the reaction of the plasma obtained from this infant before the administration of hydrochloric acid and while the child was manifesting

TABLE 8.—*Calculated Values for Calcium Ion (Ca^{++}) During Hydrochloric Acid Period Using Michaelis Modification of Rona and Takahaski's Formula*

Date	Treatment	Tetany	Bicarbonate, Per Cent. by Volume of Carbon Dioxid	p_H	Calculated (Ca^{++}), Mg. per 100 C.c.	Total Calcium in Serum, Mg. per 100 C.c.	Calculated (Ca^{++}) × Total Calcium ÷ 10, Mg. per 100 C.c.
June 5	Before HCl.....	+	52.3	7.39	2.7	5.0	1.4
7	HCl given 2 days....	0	31.9	7.22	6.4	7.6	4.9
10	HCl disc. 3 days.....	+	44.9	7.34	3.3	5.6	1.8
Average normal values.....		..	55.0	7.25	3.0	10.0	3.0

symptoms of active tetany does not support the surmise that the lowered calcium ion concentration in tetany may be chiefly the result of an increased alkalinity of the plasma. The reaction of the plasma, in this single instance, was found to be p_H 7.39; i. e., only slightly more alkaline than usual. Using this measurement and that of the bicarbonate concentration obtained from the same sample, the value for ionized calcium, calculated by means of Michaelis' modification of Rona and Takahaski's formula, is 2.7 mg. per hundred cubic centimeters and is thus not appreciably below the usual value (3 mg. per hundred cubic centimeters). The fact that the infant presented symptoms of active tetany would seem clearly to indicate that the actual calcium ion concentration was less than the calculated value, and to make necessary the assumption that the lowered total calcium has in some way interfered with the operation of the hydrogen ion and bicarbonate ion concentrations in determining the ionization of calcium. The data in Table 8 are given to illustrate the probability that the lowered calcium ion

concentration in tetany is chiefly a consequence of the diminished total calcium. Measurements of p_H, bicarbonate and total calcium obtained before, during and following the hydrochloric acid administration are given. In rough attempt to evaluate the effect of the lowering of the total calcium in determining ionized calcium, the values for the calcium ion concentration, calculated by means of the formula, are multiplied by the fraction of the usual total calcium of the plasma (taken as 10 mg. per hundred cubic centimeters) which was found in the samples taken from this subject. The values thus obtained are given in the last column of the table, and it will be seen that they are better in accord with the fact that the infant was manifesting symptoms of active tetany when the first and third set of measurements were taken.

Regardless of the question as to whether the immediate cause of the low calcium ion concentration in tetany is a more than usually alkaline reaction of the plasma or a less than usual total calcium, the formula of Rona and Takahaski explains excellently the increase in ionized calcium following an increase in hydrogen ion concentration or a decrease in bicarbonate and makes understandable the manner of the therapeutic action of substances which increase the metabolism of hydrochloric acid with the consequence that the hydrogen ion concentration is increased and that of bicarbonate lowered.

SUMMARY AND CONCLUSIONS

From a study of the effects, as regards acid-base metabolism, of administering calcium chlorid, ammonium chlorid and hydrochloric acid to an infant with tetany, the following findings may be stated:

1. The plasma bicarbonate following the ingestion of each of these substances is greatly lowered.

2. The reduction of bicarbonate is a consequence of an increased metabolism of hydrochloric acid which causes an extension beyond the normal of the chlorid content of the plasma at the expense of bicarbonate. Total base in the plasma remains closely stationary. The lowered bicarbonate is, therefore, not to an appreciable extent due to a withdrawal of base from the plasma.

3. The administration of these hydrochloric acid producing substances also causes a considerable increase in the hydrogen ion concentration of the plasma. This effect was directly demonstrated only in the case of hydrochloric acid, but may reasonably be assumed for calcium chlorid and ammonium chlorid.

4. The metabolism of these substances leads to an increased excretion of phosphates and of fixed alkali in the urine. It cannot be correctly inferred that the concentrations of these substances in the

body fluids are lowered. Their increased excretion may be satisfactorily explained as a consequence of a reduction of the volume of body water due to the diuretic action of the ingested agents.

The administration of ammonium chlorid does not raise the lowered calcium content of the plasma found in tetany. The therapeutic action of this salt may be entirely referred to an increased metabolism of hydrochloric acid, which causes a lowering of bicarbonate and an increase in hydrogen-ion concentration in the plasma, both of which alterations operate to produce an increased ionization of calcium. In consequence, a physiologically adequate concentration of ionized calcium is obtained from a lowered total calcium content. The therapeutic action of calcium chlorid and hydrochloric acid in tetany is in this respect identical with that of ammonium chlorid; but, in addition, ingestion of these substances causes an increase in the total calcium of the plasma. There is thus theoretical ground for regarding calcium chlorid and hydrochloric acid as more efficient agents than ammonium chlorid in the treatment of tetany. A relationship of the reduction of the volume of body water which follows the ingestion of these substances to their therapeutic action is not apparent.

CHEMICAL METHODS USED

The measurements of calcium and sodium in blood serum were obtained by the methods of Kramer and Tisdall,[24] and of calcium, sodium and potassium in the urine by the methods described by Tisdall and Kramer.[25] For chlorids in the serum a combination of Van Slyke's plan of precipitating the protein with picric acid and Volhard's thiocyanate titration was used, this procedure being essentially the same as that recently described by Myers and Short.[26] The same method was used for chlorids in the urine. The bicarbonate of the serum was determined by Van Slyke's method.[27] The p_H of the plasma was measured colorimetrically by the method recently devised by Cullen.[28] The p_H and titratable acidity of the urine were determined by the methods of Palmer and Henderson.[29] Urine phosphates (inorganic) were measured by Fiske's[30] method and urine sulphates (inorganic) were weighed as barium sulphate, according to the method of Folin. The total organic acid excretion in urine was measured by the titration procedure of Van Slyke and Palmer.[31] Ammonia was determined in the urine by the method of Folin and MacCallum[32] and urine nitrogen by the usual Kjeldahl method.

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THE EFFECT OF THE SPRAY PROCESS OF DRYING ON THE VITAMIN C CONTENT OF MILK

A PRELIMINARY REPORT *

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On account of the conflicting statements in the literature regarding the vitamin C content of dried milk products, and especially in view of definite statements regarding the effect of the spray process on vitamin C, a special investigation of this problem has been conducted.

This investigation was started in February, 1922. The method consisted in feeding young guinea-pigs a standard basal diet free from vitamin C. To this was added raw liquid milk or spray process powdered milk in varying amounts, these milk products being the only source of vitamin C in the diet.

The milk, both liquid and powdered, was shipped by express daily from the Merrell-Soule Powdered Milk Factory at Perry, N. Y. The milk, both raw and powdered, which was used in this experiment was taken from the mixed milk of 175 dairies representing 1,276 cows. The raw milk for feeding was drawn each day from a large vat. In order to prevent souring of the raw milk, it was cooled and shipped in sterilized vacuum bottles. The milk in the vat was pasteurized under conditions known to be favorable to the preservation of vitamin C and then reduced to powder. The powdered milk for feeding was drawn each day from this powder so that the raw milk and powdered milk came from the same lot of fresh milk. Unless this precaution is taken, a fair comparison between raw and powdered milk cannot be made, as the vitamin C content of different lots of fresh liquid milk has been found to vary considerably. The experiments on winter milk were kept separate from those on summer milk on account of a similar variation.

This difference between summer and winter milk was confirmed by the present experiment. The fact indicates that no reliable conclusions regarding the effect of drying processes on the vitamin C content of milk can be drawn unless comparison is made between the dried

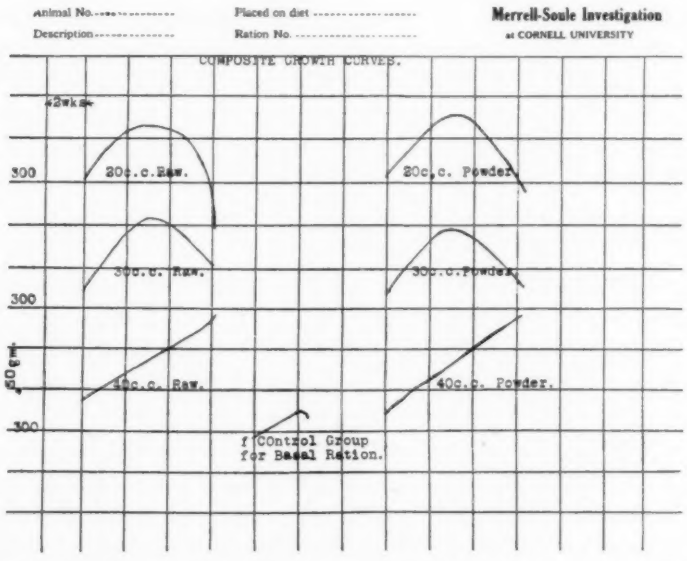
* Received for publication April 14, 1923.

* This investigation was carried on at the New York State College of Agriculture at Cornell University by George W. Cavanaugh, Professor of Agricultural Chemistry of Cornell University, and James S. Hall, under the direction and advice of Prof. R. Adams Dutcher, Head of the Department of Chemical Agriculture of the Pennsylvania State College.

milk and fresh raw milk taken from the *same* lot. Failure to take this precaution may probably account for some of the contradictory reports previously published.

PLAN OF EXPERIMENT

The guinea-pigs were arranged in groups according to the amount of milk fed, with eight or nine animals in each group. Each animal received, daily, the basal ration plus the milk to be tested, some groups receiving raw milk, others equivalent amounts of the powdered milk. The powdered milk was redissolved in water before being measured out for feeding, thus restoring it to the same water content as that of the raw milk.



Curves showing average growth of guinea-pigs in the six experimental groups and in the control group.

Careful records were kept for each animal showing daily basal ration intake, daily milk intake and body weight; also, date of development of scurvy, date of recovery from scurvy or date of death, when these events occurred. In each case of death, a necropsy was performed. This part of the experiment, in which 350 animals were used, extended over a period of seven months.

A careful study of all the groups, taking into account length of life, rapidity of growth, time of onset of scurvy and other factors indicated that milk, powdered by this spray drying process, was not inferior in antiscorbutic properties to the original raw milk. In other words, the result did not show any evidence of the destruction of vitamin C in milk powder prepared by this process.

The results of this part of the work were complicated by an epidemic of influenza in the colony, so that many animals had to be eliminated. There was also a lack of uniformity in the behavior of the animals within each group, owing apparently to the poor physical condition of many of them when received. These animals were obtained from three or four different breeders, which may in part account for the lack of uniform condition.

The experiment was, therefore, repeated. Special precautions were taken to obviate the foregoing difficulties. These may be of interest because a marked improvement in the uniformity of the results within each group and a consequent decrease in the experimental error were obtained.

All the guinea-pigs for the repetition of the investigation were obtained from the same source. Young animals were chosen from mothers that had been kept under identical conditions. These young animals had received the same food since birth. Healthy guinea-pigs weighing from 210 to 280 gm. were selected. Each one was placed at the caviary in an individual cage with some green food. They were then transported by hand to Cornell University, reaching their destination within twelve hours.

There these guinea-pigs were kept under observation for three weeks, and those that failed to grow normally were discarded. During this preliminary feeding period they received the following diet: a basal ration consisting of 60 per cent. of ground oats; 15 per cent. of wheat bran; 15 per cent. of ground autoclaved alfalfa; 5 per cent. of casein; 1 per cent. of calcium carbonate; 1 per cent. of sodium chlorid, and 3 per cent. of butter fat. In addition to this basal ration, whole milk and green grass were fed ad libitum.

At the end of the three weeks' observation period, the animals that showed normal growth curves were divided into six groups. Each group consisted of ten animals. The animals in each group received the basal ration ad libitum. In addition, they were given different amounts of raw whole milk and reconstituted Klim brand Merrell-Soule powdered whole milk according to this plan: Group 1, 20 c.c. of raw whole milk; Group 2, 20 c.c. of reconstituted milk powder; Group 3, 30 c.c. of raw whole milk; Group 4, 30 c.c. of reconstituted milk powder; Group 5, 40 c.c. of raw whole milk, and Group 6, 40 c.c. of reconstituted milk powder.

A control group of five animals received the basal ration with water ad libitum. Previous studies on the antiscorbutic properties of milk have shown that 30 c.c. is about the minimum amount that will protect guinea-pigs from scurvy. For this reason, levels of 20, 30 and 40 c.c. of milk were used in this experiment.

RESULTS

December 26, the sixty-first day of the experiment, the results showed that the average number of days for the onset of scurvy in groups fed raw and powdered milk are closely comparable.

The data obtained are given in the accompanying table.

Only five guinea-pigs of Group 5 developed scurvy, four of which have recovered. Only three guinea-pigs in Group 6 developed scurvy, all of which have recovered.

For this reason, no average time of onset of scurvy is given for these groups.

It was noted that the basal ration was apparently adequate, as the animals gained weight even while developing scurvy. This seems to eliminate complications only too common in this type of experiment in which incomplete diets are used for basal rations.

Results in Groups Fed Raw and Powdered Milk

	Average Weight at Beginning, Gm.	Average Maximum Weight, Gm.	Average Gain, Gm.	Average Time for Onset of Scurvy, Days
Control group	296	319	23	14.8
Group 1—20 c.c. raw milk	308.9	362.2	53.3	18.4
Group 2—20 c.c. powdered milk	310.7	376.1	65.4	20.3
Group 3—30 c.c. raw milk	319.6	402.6	83.0	21.1
Group 4—30 c.c. powdered milk	317.1	395.2	78.1	22.8
Group 5—40 c.c. raw milk	338.7	434.0	95.6	
Group 6—40 c.c. powdered milk	326.1	444.0	118.0	

The present part of this experiment is now in its sixty-first day. It will be continued for a total period of at least ninety days. A preliminary report is made at this time because the results seem to be concordant and to confirm the earlier and more extended part of the work.

A study of the groups at this time shows that the control group developed scurvy more quickly than the groups fed raw or powdered milk. Each group fed powdered milk did at least as well as the group receiving an equivalent amount of raw milk. So far as we can judge from data obtained from these experiments with guinea-pigs, there appears to be no destruction of the antiscorbutic properties of milk when it is thus powdered. This confirms the conclusions drawn from our first experiment; i. e., that milk powdered by this form of spray process possesses as great antiscorbutic properties as the raw milk from which it was made.

CONCLUSIONS

The results of these experiments to date indicate quite clearly that the spray process of drying milk preserves in its original strength the vitamin C; i. e., the antiscorbutic properties of milk.

The experiment is being continued to determine the effect of aging on the vitamin C content of powdered milk. So far, results indicate that spray process powdered milk probably retains its antiscorbutic properties for many months. Should this point be confirmed by the final results, its importance will be obvious. Summer milk, notably rich in vitamin C, could be powdered, and this powder could be used for infant and child feeding in the winter months, at which time raw milk is notably deficient in this vitamin.

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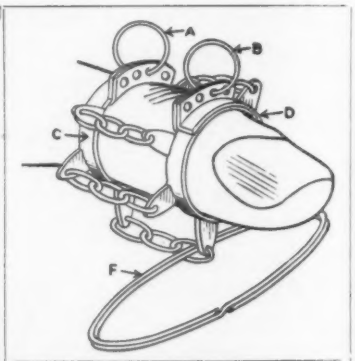

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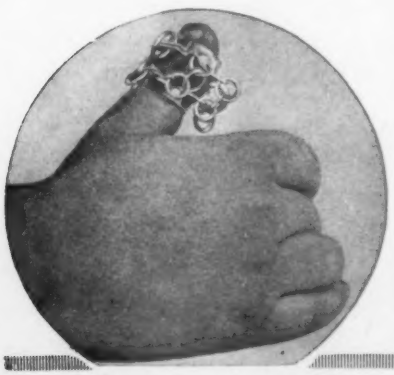

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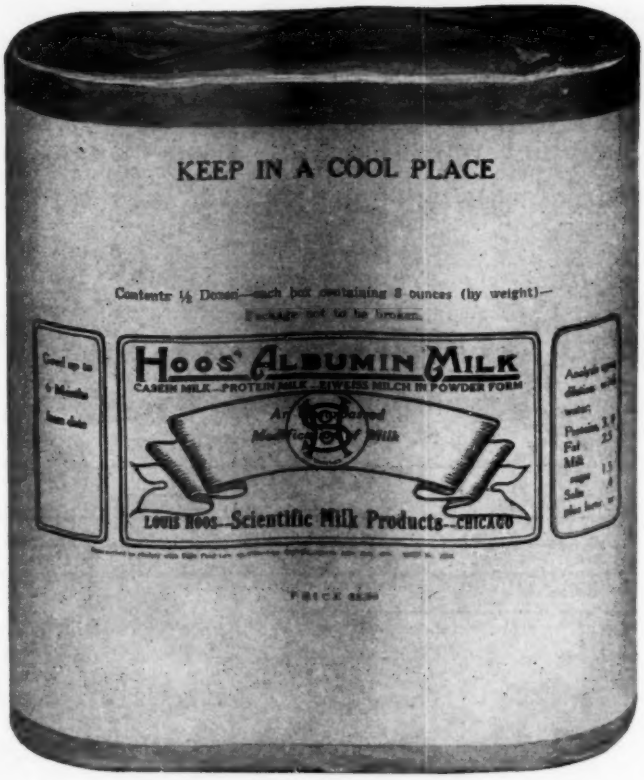
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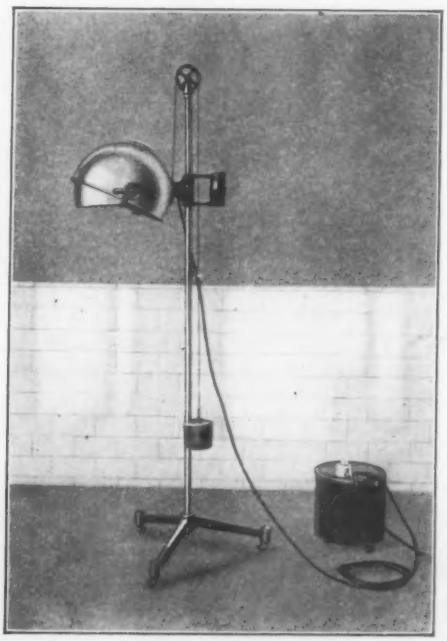

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